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ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF PULMONARY TUBERCULOSIS

By W. PARRY MORGAN

Introduction.

The treatment of pulmonary tuberculosis by means of artificial pneumothorax has of late years attracted considerable attention. Although it has proved of the greatest value where it has been adopted, it is, in this country at least, reserved chiefly as a last resort in apparently hopeless cases, after other methods have failed. As in many of these cases the results have been very satisfactory, it seems desirable to inquire why the method is not adopted in earlier and less severe cases, and whether its field of application cannot be extended. There are several reasons for this limited application. One, and the chief, is that, complete collapse being as a rule recommended, only a single lung can, in this case, be treated at a time. Again, when total collapse is undertaken, it will be necessary to maintain the collapse until it becomes reasonably certain that recrudescence will not follow re-expansion of the lung, experience teaching that such recrudescence is very serious. Further, in cases of bilateral disease, when it has been suggested that partial collapse is feasible, objection has been raised to its application to both sides at the same time that respiration might be interfered with to a dangerous extent. Lastly, the operation of introducing any gas at all into the pleural cavity is considered by many to be dangerous, and, for that reason alone, it is not undertaken by them. With a view to meeting these objections, I propose—

1. To show the possibility of attaining by partial collapse the advantages claimed for complete, and to discuss what changes take place when the gas is absorbed.

2. To show, provided there is sufficient normal tissue in the lung, that a moderate degree of collapse does not materially interfere with respiration; that is, that the method of partial collapse can be applied to both sides at one and the same time.

3. To discuss the operation and to point out how its dangers can be very considerably reduced.

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It need hardly be said that the object of inducing pneumothorax is to impose rest on the affected part of the lung, and so bring the treatment of the pulmonary disease into line with that of tuberculous disease of other parts of the body. Such rest may be relative or absolute, but the treatment is generally considered efficient according to the degree of rest obtained. Therefore what is aimed at in inducing pneumothorax is the complete immobilization of the lung, and every effort is made to attain this object. I would point out, however, that there is difficulty in maintaining a pressure sufficient to ensure complete immobilization. Pearson (1), in a typical case, has given a table of intrapleural pressures before and after each injection of nitrogen, and this shows that, even where sufficient gas has been introduced to give a definite positive pressure, within three weeks the pressure again becomes negative with respiratory variations as great and often greater than those which existed before the commencement of treatment. With such a varying negative pressure, the lung tends to expand and contract with the respiratory movements. Therefore, although the lung may be completely collapsed at the end of expiration, we cannot be sure of maintaining the collapse unless there is continuously kept up in the pleural cavity a positive pressure. As this is not done, it is clear that complete immobilization is not guaranteed, and that a certain amount of expansion is likely soon to take place. We have, therefore, to seek an explanation which is not dependent on absolute rest.

Auto-inoculation in Pulmonary Tuberculosis.

When we reflect on this subject we see that the chief object of the rest sought is to limit the spread of organisms and their products into the tissues and blood-stream; in other words, to limit auto-inoculation. It will therefore help in the elucidation of the problem to examine what is the mechanism that brings about this auto-inoculation, and how it can be modified. For this purpose we may recall certain points in the mechanics of the respiratory movements. Thus, it will be remembered that in the unopened chest the lung is elastic and expansile, and is in a state of tension which tends to make it collapse. This tension tends to separate the parietal and visceral layers of the pleurae, but, in spite of it, the lung continues to be closely applied to the chest wall, and will therefore, during inspiration, become stretched. The tension in the lung immediately below any particular point of contact of the pleurae will determine the force with which the visceral layer tends to be pulled away from the parietal, and will therefore determine the potential intrapleural pressure at that point. This intrapleural pressure will vary from place to place according to the tension in the subjacent lung. In the case of the healthy lung, no portion has lost its normal elasticity, and the lung therefore expands as a whole more or less uniformly without any undue strain in any particular part. On the other hand, in a lung containing a diseased focus, we have in the region of the focus, instead of elastic expansile tissue, a portion of lung which has become more or less an inexpansile

consolidated mass. In this condition, this part of the lung is more resistant to expansion, but the surface cannot on this account cease to be continuously applied to the chest wall. This implies that, in a radial axis through the consolidated mass, the elastic tissue, if there is any, becomes unduly stretched, and the mass itself is drawn out along that axis and, since it is not expansile, contracted transversely. In other words, the tension along such an axis, together with the intrapleural pressure at the end of it, is increased, and the mass itself is subject to deforming forces.

We could readily get a picture of what happens under these conditions by taking a sponge impregnated with colouring matter and placing it in water. If we then seized the sponge at two points, stretched and relaxed it alternately, we should see the colouring matter pumped out. In the same way, the action of the forces brought into play by the altered physical conditions in a lung when it becomes diseased is clearly to pump forcibly out of the mass with each inspiration tubercle bacilli and the products of their growth; that is, it tends to produce the auto-inoculation we desire to prevent.

Before proceeding to inquire how the condition of strain which has been described can be relieved, two points in evidence of it may be mentioned. In the first place, it frequently happens that hyper-resonance on percussion is associated with a tuberculous focus in the lung. This of course indicates a certain amount of emphysema of the lung in the neighbourhood of the focus due to the increased strain to which the tissues are subjected. Further, such increased strain tends to draw in the chest wall, an effect most clearly seen in the flattening which is so frequent below the clavicle.

The Conditions produced by Pneumothorax.

We may now examine how these conditions of strain would be influenced by a pneumothorax due to the presence of a comparatively small volume of gas in the pleural cavity. In this case, instead of the tension in the lung subjacent to any particular point in the pleural cavity determining the potential intrapleural pressure at that point, this pressure will be the same throughout and will determine the tensions in the lung. In the case of the inflated healthy lung there are no irregularities in the tension, and the shape of the lung continues, as it expands during inspiration, to correspond with that of the chest wall. The gas therefore continues to be distributed over a smooth regular surface. But in the case of a lung with a diseased focus, it is only the healthy portions that can be inflated freely without undue increase in tension. These therefore dilate and, in doing so, displace the gas which finds lodgement over the less expansile diseased part of the lung. The result is that the movements of the focus are limited, while the increased tension through it will be no greater than through any other part of the lung; also the deformation will be prevented. It is clear that the same reasoning would apply in the case of several foci, provided there was sufficient healthy lung to fill up the

increased volume of the chest when it expands, but here more gas would be required. We thus see that the effect of the introduction into the pleural cavity of a quantity of gas sufficient to produce only a partial collapse is a considerable limitation of movement of the diseased parts, and, what is more important, the prevention of that pumping action which would otherwise produce auto-inoculation; that is, we obtain by means of partial collapse the same advantages as by complete, and we should therefore expect the same results.

This thesis finds support when we compare the artificial conditions with similar conditions produced spontaneously. We shall first take the case of a pleural effusion. Except for its weight, such an effusion would act precisely in the same way as gas. Consequently, where there was a tuberculous focus in a subjacent lung, we should expect the onset of a pleural effusion to be associated with a diminution in the movements of the focus and of the forces acting on it, and that such diminution would limit, if not altogether prevent, auto-inoculation taking place. For this reason we might expect clinical improvement to follow the appearance of the effusion; and further, that if such an effusion were quickly removed, since the focus would again become subject to increased movements and deforming forces, there would be a sudden increase in auto-inoculation, with an exacerbation of symptoms. If, on the other hand, the fluid were allowed to be absorbed slowly, we might expect sufficient healing to take place while the lung re-expanded to result in the possibility of controlling auto-inoculation, and, in consequence, permanent benefit to accrue. These expectations are justified clinically. In this connexion, it is important to note that if an exacerbation followed aspiration, it would be of diagnostic significance, inasmuch as it would point to the presence of a tuberculous focus in the substance of the lung underlying the effusion. The rational treatment of such an effusion is clearly to introduce at the time of the aspiration as much gas as would be considered sufficient to prevent such symptoms.

Again, it has often been pointed out that if it is not immediately fatal, or empyema does not complicate, the presence of a pneumothorax in the course of pulmonary tuberculosis is followed not infrequently by arrest of the disease, and even by complete recovery. This, indeed, has been one of the reasons advanced in the advocacy of complete collapse, but when we remember that, where a permanent fistulous opening does not follow, the lung soon commences to re-expand, it can more reasonably be taken as ground for partial collapse, and partial collapse maintained for the comparatively short time during which the lung expands. Since, therefore, improvement appears to take place after a temporary and partial collapse, it seems reasonable to ask whether the expansion leaves the lung in precisely the same unfavourable physical condition as before. In answer to this question, I would point out that, as the gas is absorbed, those parts which are more expansile and at the same time healthier will tend gradually to fill up the space occupied, before collapse, by the overstretched lung in the neighbourhood of the lesion, and, during collapse, by

gas. Consequently, we may expect a change in the relation of the various parts of the lung to the chest wall of such a nature that the inexpansile diseased portions take a smaller share in the expansion of the lung which the movements of the chest wall bring about, than they took before collapse. A change of this sort can only be favourable since it diminishes auto-inoculation and brings this more under control.

Such a result can most clearly be demonstrated in cases where the lung has been allowed to expand after prolonged and complete collapse. In some of these cases, the diseased portions do not expand at all, the chest being ultimately filled with healthy tissue which has undergone compensatory expansion.

We are here led to inquire, if the temporary collapse produced by spontaneous pneumothorax or a pleural effusion is likely to be followed when slow absorption takes place by favourable results, why, in the treatment by prolonged complete collapse, serious recrudescence is considered to be almost inevitable when the lung is allowed to expand too soon. An explanation offers itself when we compare the effect of massage or exercise on a diseased joint that has been previously immobilized with the effects on one that has not. Such effects are greater if the joints have previously been kept at rest; and if the exercise or massage causes adhesions to break down and tuberculous deposits to be disturbed, the damage done is quite likely to be followed by a serious extension of the disease. A similar phenomenon has not infrequently been observed during the war in the case of healed septic wounds where septicaemia has followed massage and passive movements.

It is thus seen that there are good grounds for expecting the absorption of gas after a short period of collapse to be followed by a state in the mechanical conditions more favourable to healing than those existing before; also, that in such a case the risk of serious recrudescence on account of the re-expansion is less than it is after an insufficiently prolonged complete collapse.

The Effects of Pneumothorax on Respiration.

We may now pass on to consider the effects of a small pneumothorax on respiration. It will be remembered that the inspiratory movements are brought about normally by the respiratory muscles acting against the negative pressure due to the tension of the elastic tissue, but that the expiratory movements result from the contraction of this elastic tissue, and are only regulated by the respiratory muscles. The effect of a partial collapse is to diminish this tension, but not to an extent sufficient to prevent the healthy parts of the lung contracting during expiration. Consequently, while expiration continues to take place as a result of the contraction of the elastic tissue, inspiration, on account of the diminished resistance, requires less mechanical effort than before. It is clear, therefore, that were the respiratory efforts confined to the rigid chest wall, quiet respiration would become easier. But the diaphragm takes a share, so we must

inquire what is the effect of a partial collapse on it. Here the effect on respiration is due, not only to the mechanical effort put forth, but also to the extent to which the diaphragm is pushed into the thorax and kept taut. This will depend on the difference between the intra-abdominal and intrapleural pressures, and the greater the difference is, the farther will the diaphragm be pushed up into the chest when, during expiration, the muscle fibres relax. The more effective therefore will be the subsequent contraction. When the difference is smaller, the dome is shallower, and the range of movement correspondingly limited. Now, with a moderate degree of collapse, the lung is not pressed upon in such a way that it ceases to be in a state of tension. As a matter of fact, the intrapleural pressure often remains about the same as before the collapse, a condition which may be due to the average volume of the thorax increasing to accommodate the gas. The amount of collapse therefore does not necessarily correspond with the volume of gas introduced. From these considerations it is clear that the diaphragm is pushed up into the thorax practically as much as before, and does not cease to act efficiently. It is seen, therefore, that since the muscular movements are not resisted by a partial collapse, such a collapse cannot interfere to any great extent with the change in the volume of the chest which the respiratory efforts bring about.

Should the intrapleural pressure become greater than the intra-abdominal, the diaphragm would be pushed down during expiration, when the intrapleural pressure would be increasing. The contraction of the muscle fibres would in these circumstances draw up the diaphragm when inspiration took place. This inverse movement of the diaphragm, Kienboeck's sign, is well shown in all cases in which the general intrapleural pressure is increased to a large extent, and is a necessary condition if complete immobilization is to be associated with the minimum variation in intrapleural pressure.

The effect of a more complete pneumothorax on the muscular efforts is interesting and important. In this case the lung, owing to the walls of the collapsed alveoli being sticky, resists expansion and becomes therefore more or less rigid. If in such a case the intrapleural pressure is negative, there is, with the respiratory efforts, no appreciable movement in the chest wall. That a considerable effort however is being put forth would be manifested during an operation for the reintroduction of more gas by the enormous variation in the intrapleural pressure shown in these cases, a condition which must surely tend to cause auto-inoculation. Such a condition, as has already been pointed out, soon arises if the pleural cavity is not refilled in time, but it is relieved as soon as the healthy lung tissue begins to expand freely.

We now come to examine the effect of partial collapse on the ventilation of the lung. In considering this we see that any increase in the volume of the chest which takes place during inspiration will be filled in, (1) by the increase in the volume of the expansile lung, which in its turn will become filled in with a volume of air equal to that of the tidal air; (2) by the increase in volume of the gas of the pneumothorax due to the fall in the intrapleural pressure.

According to Boyle's Law, this is practically negligible, for as big a variation as 10 cm. in the intrapleural pressure would in the case of a pneumothorax of 1,500 c.c. produce a change in volume of less than 20 c.c., an amount which is a comparatively small fraction of the tidal air that passes into one lung. Therefore we may take it that, for any given expansion of the chest, the amount of tidal air is not diminished. It follows that if the amount of dead space in the air passages is not increased, and there is no reason to think that it is, the supply of fresh air reaching the alveoli and the rate at which vitiated air is removed remain practically unaltered for any given movement of the chest wall. Thus the average purity of the alveolar air remains unchanged. For these reasons, I am led to the conclusion that material respiratory difficulties following partial collapse will depend, only to the smallest extent, on the mechanical interference with the respiratory movements and on the alveolar ventilation which these movements bring about.

When we come to consider the effect of this condition on the interchange of gases through the alveolar walls, it would appear probable that the contracted healthy lung does not allow this to take place as readily as normally; but in the case of a diseased lung the conditions are not quite on a par, because here, for any expansion of the chest, a diminished expansion of the diseased portions would be accompanied by a corresponding increased expansion of the healthy, which would therefore be better ventilated. In support of this view, I may mention one of my cases in which the respiratory rate fell appreciably even during the introduction of the gas.

But even apart from these considerations, if we ask ourselves whether serious loss of function is to be expected from a partial collapse, we have only to remember that, even when very considerable portions of the lung are collapsed or for some other reason unable to function, sufficient interchange of gases take place. Evidence of this is afforded by (1) cases of bilateral pleural effusion; (2) cases of bilateral artificial pneumothorax; (3) cases of complete collapse of one side; and here the mediastinum is pushed over so as to reduce the volume of the other lung, which may be itself diseased; (4) cases of extensive double pneumonia.

Finally, in considering the function of the lung, we have to take into account the effect of nervous conditions. It is to be noted here that unless a pneumothorax is fairly complete, in which case difficulty may be due to displacement of the heart—a possibility which does not arise with bilateral partial collapse—the amount of dyspnoea bears no significant relation to the amount of gas injected, and may, so it is said, be more marked after small first injections than subsequent, even though the later ones are larger. We may, therefore, conclude that nervous causes are of no more importance in considering the effect of bilateral collapse than in the case of unilateral.

Thus, viewing the question of the interference with respiration from all points of view, I am led to the conclusion, which is confirmed by my own experience, that a partial pneumothorax will have but little effect in this

respect, and therefore, provided the operation of inducing pneumothorax can be performed in such a way that there is no risk of uncontrolled leakage leading to a more or less complete collapse, the method of partial collapse is applicable to both lungs.

The Operation.

As a preliminary we may deal with certain dangers incident to the technique, dangers which may be present even in the case of a healthy lung. They are: gas embolism, surgical emphysema, and leakage of air from the lung into the pleural cavity.

Embolism may be due to gas passing from the needle or the punctured lung into the blood-stream, such gas being incapable of rapid absorption by the blood. If, therefore, we could exclude alveolar air as a cause, we should avoid embolism altogether by the use of a gas which combines readily with the blood. Hence, for the preliminary stages, it is always advisable to use such a gas. As a rule, oxygen is recommended for this purpose; but when it is remembered that serious embolism will be due to bubbles passing through the pulmonary veins into the systemic circuit, it will be clear that carbon dioxide, which is more readily absorbed by arterial blood, is even more suitable. It has also the further advantage that it can be more readily prepared, and requires no more apparatus for its preparation than a reservoir which may be used to contain it. However, it has the disadvantage that its greater solubility in water makes it difficult to regulate the pressure. But the danger of bubbles of gas passing through the pulmonary veins under a pressure not above that of the atmosphere—and then the bubbles may consist of air from damaged alveoli—is shown by the following experiment to be very remote. Blood is aspirated into an opsonic capillary pipette until the barrel is half full. By expressing the blood on to a glass slide and reaspirating, and repeating these processes several times, we may form small bubbles of air in the lower half of the stem. If now the pipette is held upright, the bubbles will support a considerable column of blood in the upper part of the pipette; but if the portion containing the bubbles is broken off, the rest of the blood immediately runs away. The pressure which the bubbles are able to sustain can be shown by a manometer to be considerable. It therefore becomes clear that if bubbles are produced in the pulmonary veins, they will become small harmless emboli and effectually prevent movement, provided a great pressure does not drive them on. The resistance which bubbles offer to the flow of blood is illustrated by the serious cases which arise from the application of a pressure great enough to drive gas into the heart, from whence it passes as bubbles into the systemic circuit. For in these the symptoms are due to bubbles, having passed into the systemic circuit, resisting arterial pressure.

Emphysema occurs in two conditions: (1) when gas is passed into the tissues instead of into the pleural cavity; and (2) when gas in the pleural

cavity leaks out into the subcostal tissues through the puncture in the parietal pleura. This is much more likely to happen with a high intrapleural pressure.

The last danger, that of leakage of air from the alveoli into the pleural cavity, occurs when the lung is punctured.

In reviewing these dangers, it is seen that they are due to imperfections in the technique of the operation, and this I now pass on to consider.

The difficulties will be appreciated when it is remembered that the operator must carry his needle down to a point at which it will begin to separate the parietal and visceral pleurae, which are in apposition at an unknown depth, and then to verify that it has reached its proper position between these before gas is allowed to flow through. It has not been thought necessary, in the passing of the needle into the chest, to take any great precautions to prevent the lung being punctured, but, on the other hand, measures are regularly taken to verify the proper position of the needle, it being laid down that the gas shall not be

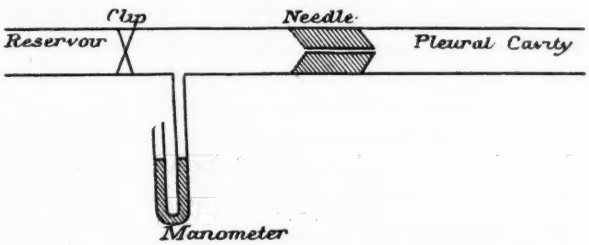


FIG. 1. Diagram showing scheme of old apparatus.

allowed to flow in until it has been inferred from the estimations of the intrapleural pressure and its variations that the orifice has passed into and lies freely in the pleural cavity. Thus it is recognized that it is, at any rate for the purpose of ensuring that the gas shall not pass anywhere except into the pleural cavity, absolutely necessary to record the intrapleural pressure and its variations, so that the problem of inducing pneumothorax with safety practically resolves itself into the problem of devising the most suitable way of arriving at the pressure at the point where the orifice of the needle rests. It has been the general practice to obtain this pressure by the direct reading of a single U-tube manometer connected by means of a T-piece with the tube which carries gas from a reservoir to the needle. This practice is open to very serious objection. In the first place, it is clear that, in order to record the intrapleural pressure and its variations by such an apparatus, the manometer must for the moment be connected only with the pleural cavity, and therefore must be shut off from the gas reservoir. Thus it is not possible to record the pressure when the gas is flowing and the operation proceeding. Again, when the gas is flowing, the manometer communicates, on the one side, with the reservoir through a tube of considerable bore, and on the other side with the pleural cavity through a fine needle. Hence the pressure recorded is practically that of the gas in the

reservoir. As the volume of this gas cannot be materially affected by the small amount of gas which, with the respiratory movements, passes in and out through the needle, the manometer will show hardly any fluctuation. Therefore when, after satisfactory pressure records have been obtained, gas is turned on, the manometer ceases to show the respiratory oscillations which indicate that the needle remains properly adjusted with its orifice in the pleural cavity. Further, when, after oscillations have appeared, gas is turned on, there is no means of recognizing whether it continues to flow except by expectantly watching the level of the water which, running into the gas reservoir, drives the gas out. Thus it is seen that this method is seriously defective, inasmuch as all the indications that are desirable for the assurance that everything is proceeding satisfactorily are wanting. But these, serious as they are, are not the only drawbacks of the method, and I shall show that the oscillations which are demanded before gas can be turned on cannot be obtained unless the lung is punctured and air has leaked into the pleural cavity.

Let us examine the steps of the operation. Before the needle is inserted, the gas is cut off, so that the manometer, communicating with the outside air through the needle, registers atmospheric pressure. This it will continue to do as the needle is passing through the tissues, but as soon as its orifice enters the pleural cavity, a movement indicating that this has taken place is communicated to the manometer. It is now presumed that if the needle is properly situated, the fluid in the manometer will commence to show oscillations, and the operation is therefore not allowed to proceed until it does. If the oscillations do not appear, even though the manometer has registered a definite negative pressure, further efforts are made to obtain them. We may therefore ask ourselves what is the condition that the variations in intrapleural pressure consequent on the movements of respiration shall be communicated to the manometer. We shall then see that this can happen only when there is aspirated into the pleural cavity gas sufficient for a requisite amount of it to be driven freely back and fore through the needle.

The question arises therefore whether this condition is fulfilled. In this connexion it is clear that, before the first operation, there is no gas in the pleural cavity, but that as soon as the needle enters it, a little is aspirated into it from the apparatus, the amount being practically equal in volume to that of the fluid which passes from the open to the closed limb of the manometer when a negative pressure is recorded. This volume is very small, and would, in a case where the intrapleural pressure stood as low as -15 cm. of fluid and the manometer tubing was of 3 mm. bore, be less than 1 c.c. But this is the amount of gas which must pass freely in and out through the needle in order to give the records of the intrapleural pressure which are demanded for safe working. As I shall show from observations made with another method, it is not sufficient, and there are reasons why this is so. In the first place, I have already shown that gas tends to move away from the region of the healthy lung, the site of election for the injection. Again, it will be recognized that, when the intra-

pleural pressure rises during expiration, if there is not much gas in the pleural cavity, the lung will tend as a valve to fall back on the needle and so block its orifice and prevent the return of the gas to the manometer. When this valve action comes into play, any subsequent rise during the respiratory period will not be recorded and the manometer fluid will remain at the same level, until, during the next inspiration, the pressure falls below that in the manometer and causes the valve to open. Thus the manometer will show diminishing oscillations and become in effect a minimum-pressure manometer, ultimately recording the lowest pressure developed during inspiration. When therefore records are obtained, there must be more gas in the pleural cavity than that excessively small volume which comes from the apparatus. There is only one other source of gas. It must be drawn in from the alveoli through punctures made in the lung.

We are now in a position to recognize two other defects of this method. In the first place, it will be appreciated that, in the initial operation, in consequence of the manometer, even when some air has leaked into the pleural cavity, tending to become a minimum-pressure manometer, the records of the pressure are likely to be too low. However, for the success of the operation, this does not make any material difference, for if there are any oscillations with a low pressure, the needle is almost certain to be satisfactorily adjusted. The second defect is serious. It is due to the danger of the needle becoming permanently blocked by blood or tissue being aspirated into it when the pressure in the manometer is low. Such an incident is not uncommon and may necessitate repuncture of the chest wall.

I shall show later how the train of events here described can be experimentally demonstrated, but for the moment will consider the clinical evidence that the lung is punctured and leaks. Such evidence is not easy to obtain even when one is on the look out for it, and for the reason that when gas is injected into the pleural cavity one is faced with the difficulty of deciding whether this gas is reinforced by air leaking from the lung.

Two of my own cases were however conclusive. In one, the operation of introducing gas was abandoned because the initial puncture was not immediately successful, but the following day there was distinct evidence of the presence of a small pneumothorax although no gas had been introduced. The second was a case in which one lung was very extensively diseased and the other commencing to be involved. All other treatment had failed, so it was decided to collapse slightly the second lung. This was done by introducing 300 c.c. of nitrogen, but it was clear from a certain amount of dyspnoea and the physical signs that the lung had leaked considerably. Aspiration to control the leak was not necessary. It is interesting to note in this case that the patient commenced to recover from the date of operation, and in due course returned to business.

I have known death follow a single injection in a case in which it was reported post mortem that the lung was completely collapsed.

Again, Clive Riviere (2), who in his recent text-book on Pneumothorax

Treatment advocates the use of the method I have just described and deprecates anything more complicated, also states that 'the effect on the physical signs of a 300 c.c. first injection is usually remarkably small, and is generally more noticeable some hours later than immediately after the operation'. However, he does not suggest my explanation that this is due to leakage gradually increasing the extent of the pneumothorax.

The testimony of Morriston Davies (3) when he says that 'a cough will considerably diminish the negative and may produce a positive pressure' also proves that leakage occurs. For it is clear that a record of a positive pressure could only be obtained by there being an increase in the volume of gas in the manometer over that originally present, the increase being equal to that of the fluid which passes from the closed to the open limb when, after the zero position is passed, the positive pressure is recorded.

The evidence on this point afforded by radiography points to the same conclusion. For while it is common for those using the method I have described to detect by radiography the presence of gas in the pleural cavity after 200 or 300 c.c. have been injected, it is my experience, since I have used my own apparatus, that it is rarely possible to detect gas until considerably more than this amount has been introduced. As a matter of fact, after the change of method was adopted in St. Mary's Hospital, Dr. G. H. Orton, to whom I am indebted for all my X-ray records, found it difficult, after his experience of the results of the old method, to believe that quantities as large as 300 or 400 c.c. had been introduced, until he had seen the new method in operation.

Failure to detect a small pneumothorax by means of radiography is really not surprising when we examine the conditions under which gas in the pleural cavity would be demonstrated. These conditions are: (1) the presence of a considerable gap between the lung and the chest wall through which rays would pass without meeting any obstacle; (2) the margin of the lung being then dense enough to throw a well-defined shadow on the screen. In regard to the first condition, it will be seen that when the lung is almost normally dilated, the shadow cast by its margin is more or less indefinite because of its close relation to the opaque ribs and of the tenuity of the dilated lung tissue, but when it becomes retracted, or is consolidated, many more rays are interrupted by it, and thus the margin thrown on the screen becomes very much better defined. Again, unless it becomes localized over a tuberculous focus, the gas in a pneumothorax will tend to spread out as a thin layer, and therefore it is unlikely that 400 c.c. spread over the extensive surface of the lung will give rise to a sufficiently wide gap and, at the same time, cause enough retraction of the lung to show up the margin in clear profile. Further, it must be remembered that when the gas is localized in such a way that there is no gap through which the rays may pass without penetrating lung tissue and so give a definite margin, the presence of such gas will not be shown at all, because, unlike the case of a cavity where there is loss of tissue, the rays have to pass through as much tissue as before, but now the gas through which they pass is outside a collapsed

lung instead of being inside a dilated one. Thus, it would seem that radiographic evidence of gas in the chest could seldom be obtained after the introduction of so small a quantity as 200 or 300 c.c., and we have justification for the conclusion that in general radiographic demonstration of a pneumothorax, after the introduction of such a quantity of gas, is possible only by this being largely supplemented by leakage from the lung.

Author's Method.

Having pointed out the defects of the method in general use, I shall now proceed to show that I have overcome them by introducing into the apparatus (1) a second manometer communicating with the connecting tube, and (2) an adjustable throttle in the course of this tube between the two manometers.

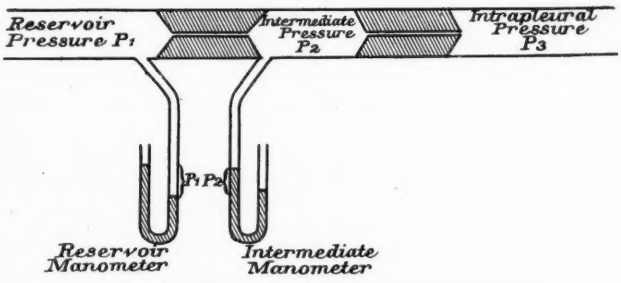


FIG. 2. Diagram showing scheme of new apparatus.

With this apparatus, it will be seen that when the gas passes from the reservoir it encounters in the adjustable throttle and the needle two resistances to its flow. As force is required to drive the gas through these, the pressure on the farther side will be lower than that on the nearer. Before the gas passes through the throttle, its pressure P_1—atmospheric pressure is taken as zero—is recorded by the manometer next to the reservoir, and this will be the reservoir pressure; then after the gas has passed through the throttle, and before it reaches the needle, its pressure is again recorded, this time by the manometer next to the needle. So long as the reservoir pressure is maintained above the intermediate pressure, it is clear that gas flows into the pleural cavity and the valve action does not come into play. Also, that when the respiratory movements are taking place, corresponding oscillations will be produced in the manometer next to the needle, but hardly at all in the other manometer, because this will continue to register the reservoir pressure. Moreover, from the relation between the reservoir and mean intermediate pressures, given by the reservoir and intermediate manometers respectively, we can readily estimate the mean intrapleural pressure, provided always we know the ratio the resistance of the throttle bears to that of the needle. (It will be convenient to speak of the mean intermediate and intrapleural pressures which are fluctuating pressures as the

intermediate pressure P_2 and the intrapleural pressure P_3.) The relation between P_1 and P_2, which are recorded by the manometers, and P_3 will depend on the fact that the ratio of the pressure which drives the gas through the throttle to that which drives it through the needle is equal to the ratio of the resistance of the throttle to that of the needle (the resistance ratio r), which within reasonable limits of error may be considered constant for different rates of flow, i.e.:

$$\frac{P_1-P_2}{P_2-P_3}=r,$$

and

$$P_3=P_2-\frac{P_1-P_2}{r}.$$

Thus, if we know the resistance ratio, we may calculate the intrapleural pressure.

A suitable ratio can readily be chosen before inserting the needle by adjusting the throttle so that P_1 bears a definite relation to P_2, for now P_3 is known to be atmospheric pressure and is taken as zero, i.e.:

$$r=\frac{P_1}{P_2}-1.$$

For example, if P_1 is twice P_2, $r=1$. In this case the intermediate pressure will, during the operation, be the arithmetic mean between the intrapleural and reservoir pressures.

If, in estimating the pressure, two consecutive results are not consistent, it clearly means that the resistance ratio has changed. This happens when the needle becomes partially obstructed. Hence we have a means of knowing whether the needle remains fully patent. It is to be noted that the estimated intrapleural pressure in such a case will be higher than the actual, so that, if the estimated is sufficiently low, we may be sure that the needle is satisfactorily situated.

The altered resistance ratio can readily be estimated by taking consecutive sets of reading at short intervals. The intrapleural pressure on any two such occasions can be taken as equal, and if P_1' and P_2', P_1'' and P_2'' be two pairs of manometric readings we have

$$P_3=P_2'-\frac{P_1'-P_2'}{r}=P_2''-\frac{P_1''-P_2''}{r},$$

and therefore

$$r=\frac{P_1'-P_1''}{P_2'-P_2''}-1.$$

In practice, extremely accurate calculations are unnecessary, the rough approximations, which, with a little practice, are estimated almost automatically, being sufficient.

It will be seen from this description that, with this method, it is not necessary at the first operation for gas to be provided from the lung in order that oscillations shall be shown in the intermediate manometer, but that these oscillations occur even when gas is passing through from the reservoir. Further,

that a flow is evidenced by a difference in the readings of the two manometers, the rate being proportional to this difference. Lastly, we can immediately make a sufficiently accurate estimation of the intrapleural pressure without having to interrupt the operation by stopping the flow of gas.

I am now in a position to describe the experimental evidence of many of my contentions, evidence that could not possibly be available with the old method. Thus I have frequently passed the needle into the chest, have satisfied myself, by estimations of the pressure and its variations, that the orifice of the needle was safely lodged in the pleural cavity, have passed quantities of gas varying from a few cubic centimetres to over a hundred, and have then found, on cutting off the supply of gas from the reservoir, that the respiratory oscillations gradually became smaller and smaller and finally stopped, the pressure recorded by the manometer sinking gradually to a minimum. In some of these cases, on the patient taking a deeper breath than usual, the recorded pressure has fallen still lower. Again, when gas has been once more turned on, it has been the rule for the oscillations to recommence, but in some cases in which they have failed to appear I have afterwards found the needle blocked.

From these observations I think we can clearly draw the following conclusions:

1. Gas introduced into the pleural cavity will often move away from the needle.

2. If it moves away and more gas does not continue to flow in from the reservoir, the valve action of the lung comes into play, cutting off the manometers from the pleural cavity.

3. In such cases the old method could not possibly come into application and oscillations appear in the manometer except by the aid of gas which leaked, and leaked continuously, from punctures made in the lung.

The practical details of the use and a description of my apparatus as made by Allen and Hanburys I do not propose to give here. They have been fully described in the *Lancet* (4), to which journal I am indebted for permission to make use here of my papers (5) on pneumothorax.

Before concluding, I should perhaps just refer to the clinical side of the subject. Unfortunately, the War has interfered with my opportunities in this direction, so my records are not as numerous or as complete as I should like. I am unable to indicate definitely how much gas should be used or how often it should be injected. It would seem that absorption takes place more rapidly in the case of partial collapse, so that while treatment is continued, more frequent injections are required. As a rule I have injected about 300 c.c. at the primary operation, and in cases where bilateral collapse was induced, on both sides at the same time, provided I have succeeded on the first side without difficulty. Afterwards, at intervals of a week to a fortnight, I have given up to 500 c.c., provided the amount given did not produce a positive pressure. For how long the treatment should be continued, it is impossible to say, but I have not gone on with it for more than two or three months. As

a matter of fact, two of my most striking cases were those in which the collapse was quite temporary, and in these it appeared to save the patient. One has already been referred to. The other, which was my first case, I treated in 1912 in South Africa. I ventured to induce bilateral pneumothorax in this case only because the patient had been given up by his regular medical attendant. Writing at Christmas, 1916, he gave a very satisfactory report of himself. In the case of my other patients, repeated injections were given, some of them bilaterally, and in no case can I say that the course of the disease was adversely affected. In most of them there was definite improvement which was maintained after the treatment was discontinued. Since the War commenced I have not been able to follow up these cases.

My experience, therefore, although it proves the practicability of inducing a moderate degree of pneumothorax bilaterally and leaves me hopeful regarding the utility of partial collapse, is too limited to justify me in attempting to give a definite estimate of its value, and I would do no more than commend it for consideration. In doing so, I am conscious that many cases will be unsuitable. In some, the disease will be too widespread for differential rest to be possible; while in others, adhesions will render an efficient collapse unobtainable.

I am conscious, too, that many writers have expressed strong views regarding the inefficiency, as a method of treatment, of an incomplete collapse, but I would suggest that these views are based on the experience of the advanced cases in which satisfactory differential rest is impossible, or on the experience of the cases in which the collapse, although not complete, is as near being complete as possible, and therefore so great as to prevent the free expansion of the normal lung tissue.

Therefore I would submit that the objections that have been raised are not based on experience, and consequently that, if the method is sufficiently reasonable to commend itself, I am not called upon to meet them until such experience has been obtained.

Finally, I would express the hope that this will not be delayed as long as it was in the case of complete collapse, for whereas it is only in comparatively recent years that its utility is really being recognized, it was in 1820 that Dr. James Carson (6) first proposed pneumothorax for the treatment of pulmonary tuberculosis, and in regard to it said, 'Whether the method proposed will be found practicable or, if practicable, to the desired extent beneficial, or whether, as will be supposed by far the most probable, it may amuse for the moment and then, like all its predecessors, sink into deserved neglect are questions which must be left to the decision of time. Whatever may be the event, I shall have this consolation, that I incur no risk in this case, by any proposition that may be made, of diverting the current of inquiry into a channel that shall be less productive than any of those in which it has hitherto run.'

Conclusions.

1. Partial collapse of a tuberculous lung tends to give rest to any consolidated portion, and thereby to reduce auto-inoculation.

2. The changes which take place as a result of the absorption of gas tend to reduce the amount of strain in the diseased parts when this strain is compared with that which existed before collapse. A single operation for collapse is therefore likely to be followed by good results.

3. A moderate degree of collapse does not materially interfere with respiration provided it allows sufficient normal tissue to function.

4. Both lungs can be treated at one and the same time.

5. In all cases of aspiration of fluid from the pleural cavity, the fluid removed should be replaced to some extent by gas. This is desirable, in the case of tuberculosis of the lung, in order to give rest to the diseased parts, and, generally, because it prevents the valve action of the lung and all that distress which would result from attempts to empty the cavity completely.

6. The apparatus and method usually employed for the operation are seriously defective in many respects, and necessitate the puncture of the lung and leakage of air from it.

7. The defects can be remedied by the use of a slightly more elaborate apparatus.

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A SIMPLE RAPID METHOD OF ESTIMATING THE FILTRATE NITROGEN IN SMALL QUANTITIES OF BLOOD AND OF OTHER BODY FLUIDS

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Plan of the Article.

[The numbers quoted after the topics refer to the paragraphs.]

Apologia and introduction: 1 to 4. The method outlined: 5. Taking the sample of blood. Suggested detail in the pointing of hypodermic needles. Use of stylet in exploring: 6. Mixing serum and clot with 'acid brine': 7. The rapid method of precipitating the proteins and centrifuging in two stages is economical of blood and of expensive reagents and obviates tedious diluting, filtering, and evaporating: 8 to 10. The final precipitant. The advantage of phosphomolybdic acid over phosphotungstic acid: 11 to 13. Methods and importance of deproteinating cerebro-spinal fluid: 14. Proteins in contact with mineral acids gradually split up, forming nitrogen-yielding amino-acids: 15. Ammonia and creatinin are represented in the filtrate nitrogen by this method: 16. Accuracy of the hypobromite method with rapping and simple delicate measurement: 17 to 21. *Coup* and *contre-coup* illustrated *in vitro*: 18. Convenience and accuracy of drop-measuring small quantities of test solutions: 22. Nitrogen latent in supersaturated solution: 23. Preparation and care of the bromine lye: 24. A safer injecting pipette and a steady method of using the teat: 25. Known factors maintaining health-lowness of filtrate nitrogen in the blood: 26. Working summary: 27. Calculation of result illustrated: 28.

1. *The importance of an estimate of the nitrogenous waste in the blood* as an aid to diagnosis and to treatment is becoming more and more recognized. The estimation of the urinary urea in a twenty-four hour sample, however valuable it may be as an additional test, is no substitute for the blood test. Indeed, as is known, the urinary nitrogen in a case of nephritis (1), after being for some days less than the diet nitrogen, may become, in presence of the accumulating blood filtrate nitrogen, actually greater than the diet nitrogen, and may thus be deceptive rather than informative. The simple method described below may serve in the meantime a useful purpose of progress.

2. The method was devised in the course of some work that I have been doing on the retained nitrogen in various specimens, principally blood and cerebro-spinal fluid, obtained in the wards and in the post-mortem room. The

work began in 1913 in the cytological examination of cerebro-spinal fluids (2) in connexion with the research on parasyphilis (3) made by Dr. Head and Dr. Fearnsides with Dr. McIntosh and Dr. Fildes. In fixing a drop-film of an extra cerebro-spinal fluid overheating produced ammoniacal fumes, indicating to me the presence of urea in considerable quantity, which hypobromite estimation then showed to be about $\frac{1}{2}$ per cent. For comparison other cerebro-spinal fluids were similarly examined.

3. But the body-fluid that can generally and justifiably be obtained for a filtrate-nitrogen test is, of course, not the cerebro-spinal fluid but the blood. My opportunity of obtaining bloods in sufficient quantities for comparative investigation came with work in the post-mortem room during war-time. The blood, however, contains much coagulable protein, which pretty effectively hinders the easy success that was, in the case of cerebro-spinal fluid, attained by treating the merely centrifuged fluid with hypobromite solution. And even in the case of cerebro-spinal fluid the omission of deproteination may, as shown in Par. 14, lead to a result far from accurate.

4. To eliminate these protein constituents, or to circumvent them, there have been devised various processes, none of them apparently simple and rapid enough for use by the busy practitioner or for use on behalf of the house physician anxious to lose no time in beginning the best treatment of a patient just admitted suffering perhaps from uraemia, perhaps from one of its *pathomimes*. In such a diagnostic emergency the method of this article would promptly enable the laboratory worker to give valuable information. Accordingly, at the request of esteemed advisers, the method is here set forth, although the publication of the cases with macroscopic and microscopic findings must in the circumstances be delayed.

5. The method consists in precipitating the proteids, centrifuging instead of filtering, and then testing the clear centrifugate by an efficient hypobromite process. The method may first be described without the discussion of details. The proteins are eliminated in two simple rapid stages. First, the blood in a centrifuge tube is mixed with its own volume of a saturated sodium chloride solution in 6 per cent. sulphuric acid or in a mixture of nine-tenths of 6 per cent. sulphuric acid and one-tenth of 6 per cent. phosphoric acid. (This latter-mentioned acid brine, with phosphoric acid, secures the non-precipitation of ammonia by phosphomolybdic acid and also suits phosphotungstic acid, mentioned below.) Centrifuging now gives a slightly opal or even a clear centrifugate almost free from proteins and occupying 60 to 70 per cent. of the total volume. A suitable volume of this centrifugate is measured by a graduated pipette into a second centrifuge tube and is mixed with about one-tenth volume of 10 per cent. phosphotungstic acid or of 10 per cent. phosphomolybdic acid. Another short centrifuging now gives a clear liquid. 1 c.c. of this is treated in a ureometer and rapped as described in Par. 18. A provisional reading can be reported within about twenty minutes of the time the blood was received, but for accuracy another half-hour is required.

6. *The specimen of blood* may be taken by the well-known method of congesting the forearm by a couple of turns of bandage above the elbow, the patient also if possible clenching the fist and slightly flexing against resistance the elbow to throw up the semilunar fascia with the median basilic vein superficial to it. The needle of a hypodermic syringe previously boiled in water (oil being undesirable in the bromine lye) is inserted into the vein through the iodine-painted skin and the blood is drawn off. Even 1 c.c. will serve for a test. Then the bandage is released before the needle is withdrawn and the puncture is sealed with a shred of sterile cotton-wool soaked in collodion. The blood is at once expelled into a sterile tube and the syringe is without delay washed out with water.

Here may be mentioned an important detail in *the pointing of such hypodermic needles and tapping needles* as are used without a stylet ground off to exactly the same point-slope. In order to prevent the complete punching out of a wad of skin, or at least the shaving off of the surface layer, which may then be carried into and left in the wound, the sharp inner edge of the hinder end of the oval obliquely ground needle-section ought to be smoothly blunted by a hard steel wire longitudinally grooved, like a butcher's steel, by being steadily drawn over a carborundum stone. The partly outlined tag of skin will then be left attached to the surface and not noticeably scraped.

In *the taking of cerebro-spinal fluid* the puncture may be made either as usual between two laminae or else, if 'abdominal examination only' in the cadaver is permitted, through an intervertebral disk. Blood admixture may be minimized by passing down the hollow needle an exploring stylet with smooth round point and with known excess of length over the hollow needle. If the hollow needle-point is in the spinal canal the exploring stylet can be pushed onward freely till the blunt point gently touches the anterior wall of the spinal canal. The 'excess length' minus the length now projecting behind the hollow needle indicates how far the hollow needle-point is from the anterior wall of the canal. Outflow of fluid in the cadaver can be secured by injecting air from a syringe applied to a needle passed into the cervical canal—as mentioned by Bigelow, *American Journal of Insanity*, lxvii. (1911) 745.

7. *Blood or serum or even blood-clot* may be used with the same result, except that the more blood-cells the more deposit and the less free centrifugate. Serum is readily mixed with the acid brine to a flowing paste of discrete clots by closing the mouth of the centrifuge tube with the thumb covered with a small square of smooth washed rubber and inverting two or three times. Clot is pretty easily mixed with the acid brine by grinding it round against the wall of the cylindrical centrifuge tube with a glass rod. Blood-clot, when tried to confirm its admissibility for the test, was by thrusting it with the squarely broken end of a glass tube easily cut up to a paste, yielding a level surface for measurement of the volume of acid brine required (Par. 27).

8. *Precipitation of the proteins* in the two simple stages as recommended allows economy of expensive metals, now especially employed for grimmer

purposes, and of sometimes scarce patient's blood. The acid brine described in Par. 5 was found to be the most efficient and convenient of a number of mixtures of neutral salts with mineral acids. Also in the preliminary stage it is far better than either of the two expensive acids. Used in a mixture of 1 c.c. of blood with 1 c.c. of precipitant it was found to yield a much more tractable deposit and considerably over 1 c.c. of centrifugate, that is, more than three times as much centrifugate as yielded by the expensive acids. In the second stage precipitation is completed (Par. 5) with about one-twentieth of the proportion of phosphotungstic acid prescribed in the Schöndorff method (4).

9. *The preliminary centrifugate* yielded by the acid brine may, if desired, be at once treated in the Doremus ureometer, when it usually gives a reading higher by about one-tenth of itself than the reading given after the final precipitation of the centrifugate. From some bloods the preliminary centrifugate may be so clear and so protein-free as to cause no froth in the ureometer.

10. The addition of the final precipitant after coagulation of the blood by the acid brine but before centrifuging was tried. It does not, however, give a clear centrifugate. But after admixing a little more of the final precipitant and centrifuging again the liquid is clear. The clear precipitation of proteins, whether with or without boiling, is a 'tricky' task. But the above recommended technique seems to succeed uniformly with *a minimum* alike of *time, of blood, of reagents, and of mess.*

11. The *final precipitant solution* may now be further specified. Phosphotungstic acid and phosphomolybdic acid are precipitated along with the proteids, but any excess remains in the centrifugate. Now, although such excess does not seem to affect the hypobromite result, nevertheless a deficiency does. And phosphomolybdic acid has over phosphotungstic acid the advantage that, when all the protein has been precipitated, a slight excess of the yellow phosphomolybdic acid gives to the centrifugate a yellow tinge readily reduced to an even more noticeable blue colour in the precipitate and later in the centrifugate. Incipient reduction in the stock of phosphomolybdic solution, indicated by its showing instead of a pure canary yellow a greenish yellow, may be corrected by the cautious addition of one or more drops of hydrogen peroxide 'ten volumes' solution with warming till the pure canary yellow reappears. A satisfactory reagent was prepared by digesting, with boiling for an hour, 10 grm. of pure molybdic acid with 40 c.c. of distilled water and 8 c.c. of 66 per cent. phosphoric acid, then making up the solution to 106 c.c. and bringing the colour just to pure canary yellow with a few drops of H_2O_2 solution. The small amount of the acid left undissolved at this stage gradually dissolves.

12. The presence of *nitric acid in the final precipitant* seems inadmissible in view of the action of possibly produced nitrous acid on urea. Also the presence of *ammonia in the acids* must be looked out for. Indeed, each of the reagents used in the process, as also the laboratory water, ought to be tested by the hypobromite solution as described in Par. 24. Also all tubes and pipettes

ought to be rinsed just before use. *Precipitants ought to be pipetted from the bottle.* The bottle lip must not be left wet with acid solution, which would absorb ammonia.

13. The 10 per cent. solution of some commercial phosphotungstic acid gives a slight crystalline precipitate with the preliminary precipitant solution described in Par. 5, while longer-kept solution of another sample gives no such precipitate. But each kind acts efficiently as the final precipitant with the technique described. When used, e. g. in cerebro-spinal fluid or in ascitic fluid, without preliminary precipitation by acid brine as mentioned in Par. 14, the final precipitant (either phosphotungstic acid or else phosphomolybdic acid) ought to contain some extra mineral acid, e. g. 6 per cent. of phosphoric acid.

14. Cerebro-spinal fluid may be so well freed from protein by an equal volume of the acid brine that the filtrate nitrogen then found in it is approximately the same as that found after further treatment with phosphotungstic acid or with phosphomolybdic acid. But in cerebro-spinal fluid, just mentioned, and in some ascitic fluids treatment with acid brine is not as necessary as it is in the case of blood: the small amount of protein present may be practically eliminated by direct treatment with about one-tenth volume of phosphotungstic acid or better of phosphomolybdic acid, which latter acid, as explained in Par. 11, indicates when all the proteins are precipitated by it. Small as is the amount of protein in cerebro-spinal fluid, *the removal of the protein before treatment with hypobromite* is very important. Without deproteination a cerebro-spinal fluid, although centrifuged clear, may give a hypobromite reading more than 70 per cent. higher than that given by the cerebro-spinal fluid after treatment with simple acid brine. The actual percentages in my latest experiment on this point were 0·12 per cent. as against 0·07 per cent. (Different careful experiments by Barcroft had already, I find, suggested the important fact just stated. Cf. Par. 16.)

15. *Hydrolysis of the coagulated proteins* left in contact with 3 per cent. mineral acid gradually takes place, forming amino compounds that, on treatment with hypobromite, yield nitrogen. This was shown, e. g., by the blood from a man dead with contracting white kidneys, streptococcic peritonitis, and phlegmonous gastritis. On the evening of the post-mortem day the blood after preliminary precipitation with acid brine showed 0·19 per cent. of filtrate nitrogen, and after the final precipitation with phosphotungstic acid practically the same percentage of filtrate nitrogen. After six weeks in contact with the deposit, but of course not evaporating, the 'preliminary centrifugate' without further treatment showed 0·29 per cent. of filtrate nitrogen, and after precipitation with phosphotungstic acid only 0·26 per cent. of filtrate nitrogen. Although I could not in my method detect appreciable rise of the filtrate nitrogen in specimens left experimentally on the deposit for twenty-four hours, yet filtration methods demanding twenty-four hours' contact with fairly strong mineral acids may possibly run some risk of a rise.

16. *Ammonia and creatinin are included in the filtrate nitrogen* by this

method. Abderhalden (5) says that in the Pflüger-Bleibtreu method (applied to urine) phosphotungstic acid precipitates creatinin and ammonia along with albumin, uric acid, and purin bodies. But in several controlled experiments first with ammonia and then with creatinin, added to blood before precipitation, whether with phosphotungstic acid or with phosphomolybdic acid, I found the ammonia required by calculation and by the controls fully demonstrated in the centrifugate and the creatinin as required by the controls present in the centrifugate. Ammonia being the direct representative of urea, the inclusion of its nitrogen in the filtrate nitrogen is desirable, especially if, as usually, only one test, that for filtrate nitrogen, can be obtained. In Barcroft's original paper ('The Estimation of Urea in Blood', *Journal of Physiology*, xxviii. (1902) 232), seen by me since the above was written, this inclusion of ammonia nitrogen with urea nitrogen is urged. Barcroft's method uses 1 c.c. of blood but requires 70 c.c. of absolute alcohol, which all has to be filtered and then evaporated in a 5 c.c. capsule at 65° C., and demands for its completion more than twenty-four hours.

17. The blood filtrate thus deproteinated, and whether filtered in large quantities or thus centrifuged in small quantities, may be treated by various processes for various purposes. But for estimation of the filtrate nitrogen *the hypobromite method* has advantages. It is familiar and so easy that even the busy practitioner could in an emergency himself undertake it. Moreover, it is a gas-volumetric method carried out on a planet where liquids are ordinarily largely saturated with the very gas. *With the modifications prescribed below* it can be made to measure with consistent accuracy urea and the like in quantities so small as those of the experiments described in Par. 21. These modifications consist in (1) rapping the ureometer tube to concuss the apparently supersaturated solution of nitrogen, (2) accurately but simply measuring the small quantities of nitrogen evolved, (3) the avoidance of washing with water, (4) the use of suitably fresh non-autolytic hypobromite in sufficient quantity.

18. The effect of *rapping the ureometer* during a urea-decomposing experiment was specially observed. The Doremus type of ureometer is convenient; its form facilitates rapping, it contains no loose glass tube, and it may have a tube tapered to display small quantities of gas. Such a ureometer was filled with fresh bromine lye as described in Par. 24. Then 1 c.c. of $\frac{1}{2}$ per cent. urea in 3 per cent. H_2SO_4 half saturated with NaCl was injected as described in Par. 25 and the whole was left for thirty minutes. By this time evolution of gas had ceased and the result, 0·435 per cent., seemed ready for noting. Now the ureometer was held in one hand and was sloped 20° or 30° towards the horizontal, so that the shorter limb was raised to prevent air passing back round the bend, and the wall of the lowest part of the longer limb was rapped a few times sharply but judiciously with a piece of soft pine. In a few seconds ensued changes showing the gaseous supersaturation of the column of bromine lye, and incidentally illustrating *in vitro* the phenomenon of *coup* and *contre-coup*. At the site of concussion and at the opposite pole of the circle of the tube's cross-

section, where the concussion wave breaks and rebounds, arose tiny bubbles of gas in clouds like distant shrapnel bursts. When these had risen high enough to avoid loss, the tube was momentarily tilted, to allow the large bubbles of gas to approach the bend and to mix fresh bromine lye in the uppermost layers, where lay any undecomposed lighter solution. Fresh rapping set the whole column effervescing and caused the volume of collected gas to rise from 0·435 to 0·525, the liquid now no longer gassing on rapping. Further tests with another $\frac{1}{2}$ per cent. solution of urea previously dried over $CaCl_2$ gave sensibly the same result. Also 1 c.c. of a $\frac{1}{20}$ per cent. solution of the same urea gave 0·052 per cent. of gas. Tests with $\frac{1}{2}$ per cent. and with $\frac{1}{10}$ per cent. NH_4Cl solutions gave corresponding results. The graduation of these readings was on the basis of 380 c.c. of N at 20° C. per 1 grm. of urea. Accordingly for the purposes of this method this basis will have to be abandoned for the basis of practically 400 c.c. of N at 20° per 1 grm. of urea.

19. *Rapping the ureometer* before injecting the urea solution, to detect for rejection any bromine lye undergoing autolysis, and also before reading the gas volume, seems as sound a procedure as is wetting and squeezing out a sponge before and after using it to bail out the liquid in a cavity. Without the trustworthy help given by it I would not presume to estimate with correctness the small quantities of filtrate nitrogen concerned in this research. Rapping was found to raise a gas bubble that after thirty minutes was 4 mm. in diameter to 6·5 mm. in diameter and of nearly proportional depth, that is, to raise the reading by over 200 per cent. (Cf. Par. 21.) Without rapping, to bring the reaction to a definite end, the bubble of collected gas would probably keep on slowly and uncertainly increasing for many hours. That the gas actually liberated without rapping is but a mere fraction of the due amount probably accounts for the smallness of the various volumes allowed for by the graduation marks in Doremus ureometers for the first tenth per cent. compared with, say, the fifth tenth. To avoid the very considerable and apparently inconstant errors involved by the use of the ordinary hypobromite method for small percentages of urea—errors much greater than those that arise in estimating the comparatively huge urea content of urine—I used constantly the rapping technique and reckoned first from the dimensions of the gas bubble, as measured in the ureometer by a millimetre rule in a suitable light (shining on the lower part of the ureometer tube and reflected up to the shaded upper part), and then from the volume occupied by the gas when transferred under water at room temperature to a taper-ended centrifuge tube graduated with the due quantities of mercury. In transferring the larger lots of gas an inverted small funnel was used, and always air-bubbles adhering to the funnel and to the collecting tube were avoided. (Cf. Par. 20.)

20. This measuring tube, about 5 mm. in diameter at its narrowest, and there nearly as small as capillarity will allow to be used, affords fairly accurate measurement of small volumes of gas. As the delicacy of such a measuring tube is quadrupled by halving the diameter of the tube, a tube in a ureometer for

small percentages ought to be thus tapered. In reading the gas the measuring tube or the ureometer may be lowered into water of noted temperature.

21. *Control experiments* done *with various small known amounts* of urea and of ammonium chloride showed that the process is fully good enough for clinical purposes. For instance, $\frac{1}{45}$ c.c. of a stock solution of 5 grm. NH_4Cl in 22 c.c. water was measured as two drops from a small pipette, quickly drawn and gauged to Morse 76 (Par. 22), into 10 c.c. of tap-water. One c.c. of this dilution, in bromine lye that had been previously tested by rapping, acted as detailed in Par. 18. The gas bubble, 6·5 mm. × 5 mm., contained about $\frac{13}{2} \times \frac{13}{2} \times \frac{5}{1} \times \frac{11}{21}$ c.mm., i.e. about 110 c.mm., or some 5 per cent. *lower* than the amount theoretically expected, namely $\frac{1}{45} \times \frac{1}{10} \times \frac{5}{22} \times \frac{14}{53{\cdot}5} \times \frac{11{\cdot}2}{14} \times \frac{1000}{1} \times \frac{293}{273}$. The experiment repeated next evening produced a bubble judged to be 7 mm. × 5 mm., which was found by the above calculation, done some days afterwards, a little *higher* than was expected. I am repeating these and other control experiments, as circumstances permit, with more precision of injecting method. Melting a little hard paraffin on the tip of the injecting pipette helps in this direction.

22. The just-used *drop-method of delivering*, as accurately as simply, $\frac{1}{50}$ c.c., or less, of the NH_4Cl solution is described in my articles in the *Lancet* of December 4, 1915, ii. 1243, and September 2, 1916, ii. 423–9. When the first ureometer experiment described in Par. 21 had been set going the Morse 76 pipette was found, by dropping into a special usable gauged small measure-flask,[1] to yield a fraction over 90 drops per c.c. at 21° C., showing that the error in thus measuring is less than $\frac{1}{2}$ per cent. A larger dropping pipette similarly made may be kept for measuring the final precipitant and may be passed through the cork of the small retail bottle. But phosphomolybdic acid and phosphotungstic acid must not be allowed to touch cork or other reducing matter.

23. *The concussion-liberation of gas* has apparently not been mentioned heretofore, but it *is of high importance*, preventing as it does a loss of from 6 per cent. to hundreds per cent. on the volumes of gas actually obtained by the hypobromite process without rapping. It seems to be usually due to the breaking up of a supersaturated gas solution. But some of it, especially in the slow prolonged gas-liberation noticed in a blood with experimentally added creatinin, may be due to acceleration of slowly progressing chemical action.

24. The *bromine lye* used was weaker than that ordinarily used, but the charges of urea solution were small and dilute and were introduced slowly up a considerable depth of the bromine lye. The caustic soda solution contained 1 lb. in 2 litres, i.e. '$22\frac{1}{2}$ per cent.' Of this 220 c.c. were used with a 2·2 c.c. capsule of bromine and served for nine ureometer fillings to just beyond the bend. Thus seventy-two capsules used in war-time served for over 600 tests. Washing out the ureometer with clean water just before filling was utterly avoided, as was also any diluting of the soda lye or of the bromine lye with clean water just before use. Any admixture of unboiled tap-water caused, especially on rapping, disengagement of gas up to 2 c.mm. of gas per 1 c.c. of

[1] Procurable from Messrs. R. B. Turner & Co., 9–11 Eagle Street, London, W.C.

water. As 2 c.c. of the same tap-water when boiled and cooled produced no visible gas in an hour with occasional rapping, probably tap-water is a better solvent of air under water-supply pressure than is bromine lye of air at room pressure. Overnight the ureometers were left filled with used bromine lye even if it was water-mixed. If required for use shortly after immersing in tap-water, the ureometer was drained out, then rinsed out with bromine lye, then filled with fresh bromine lye and stood for half an hour or longer with occasional rappings till no further gas was evolved. Bromine lye, after being made and cooled in water, is preferably shaken with air and left for an hour or so before use.

25. The *pipette with curved point* for injecting the urea solutions into the Doremus ureometer may, for the purpose of rapid thorough washing, have its point-bore rather larger than is usually provided. This, of course, will increase the danger of injecting a bubble of air after the last portion of the urea solution. But in the pipettes that I made for the purpose I arranged that the 1 c.c. volume and the ½ c.c. volume should extend from the respective upper marks, not to the aperture but to a point some distance above the aperture. The solutions of urea in this test are so dilute that the meniscus of the solution in the pipette near the point can be clearly seen. And *the easy steadiness* always desirable in working with a teated pipette can be secured by using the method described in my paper in the *Lancet* of 1915, ii. 1243, par. 11 : 'The teat, of ample capacity, is best managed, not by having the worker's finger and thumb vibrating on the unsteady inflated teat-walls, but by steadying the ulnar edge of the thumb against the radial edge of the forefinger with the teat fundus collapsed between them, compression of the teat being accomplished by rolling more and more of the thumb pulp over the forefinger pulp and inflation by rolling contrariwise.' The graduation of the pipette can be managed by weighing into or by delivering from a tested pipette into a small paraffin-coated tube 1 c.c. or ½ c.c. of water, then drawing the water into the previously filled and emptied new pipette till the lower meniscus of the complete quantity is at the desired point, the marks lower and upper being made first with ink, then by scratches annealed by heating to less than softening point.

26. In this preliminary note I do not attempt to mention the cases on which I have made some investigation. I would merely remind the reader that the normal lowness of the filtrate nitrogen in the blood seems to depend on three factors : (1) A sufficiency of healthy kidney tissue, (2) sufficiently maintained or compensated circulation of blood through the kidneys, (3) a sufficient supply of water to the blood to allow a sufficient excretion of urine through free passages. For instance, in children factors (1) and (2) are usually so good that their health percentage of filtrate nitrogen seems smaller than the 0·035 per cent. of filtrate nitrogen stated as the general health limit. Finding in the blood taken at the autopsy of a baby admitted dying of diarrhoea and vomiting, but not yet emaciated, some 0·18 per cent. of filtrate nitrogen is like hearing a post-mortem echo of the cry of the child's system for water. Such subimbibitional hyper-

nitraemia will, of course, be allowed for by an observant medical attendant. And as for factor (2) the 'heart kidney' seems to maintain the excretory function wonderfully well. But when factors (1) and (2) co-operate in failure, as, for instance, when with insufficient kidney tissue the circulation fails, then the filtrate nitrogen may rise to 0·2 per cent. and higher, much as in acute nephritis with increased blood pressure. On the whole the test affords always a valuable and sometimes an invaluable addition to the objective data for the clinician's skill to work on.

27. An *outline of the method* is given in Par. 5. A *working summary* is here added.

Apparatus and reagents required:

Ureometer of specially modified pattern (Par. 20), with curved pipettes marked for 1 c.c. and for ½ c.c. (Par. 25). These are made by Messrs. R. B. Turner & Co., 9–11 Eagle Street, London, W.C.

Or an ordinary pattern Doremus ureometer with the help of a graduated centrifuge tube and a millimetre rule (Pars. 19 and 20).

A centrifuge is almost indispensable.

'Acid brine', i.e. saturated NaCl solution in a mixture of nine parts of 6 per cent. H_2SO_4 and one part of 6 per cent. H_3PO_4 (Pars. 5, 8).

'Final precipitant', i.e. 10 per cent. solution of phosphomolybdic acid or of phosphotungstic acid (Pars. 5, 8, 10–14). Drops of these acids, each about $\frac{1}{40}$ c.c., may be delivered by a Morse 52 pipette (Par. 22).

Procedure:

The sample of blood is received presumably in a test-tube (Par. 6).

Fill a ureometer with bromine lye (Par. 24). Into a centrifuge tube, preferably cylindrical, pipette 1 c.c. of blood, add 1 c.c. of acid brine, mix as described in Par. 7, and centrifuge. Of the centrifugate pipette off 1 c.c. into a fresh centrifuge tube, admix four or five 'M 52' drops of the final precipitant, and again centrifuge briefly. Of the clear final centrifugate inject 1 c.c. into the prepared ureometer and rap occasionally (Pars. 18, 19). Read provisionally after say ten minutes, and finally after forty-five minutes. The quantity, whether of blood to start with or of the preliminary centrifugate, may with advantage be more than 1 c.c., with of course a due proportion of the reagents concerned. And even if not quite 1 c.c. of blood is procured, a useful test may be done: mark the upper level of the sample on its test-tube, transfer all the sample to the centrifuge tube, pipette in acid brine to the mark on the test-tube, and add it to the centrifuge tube.

28. The *calculation* may be *illustrated* from the case of a physically healthy man of thirty-six killed suddenly by a high fall. Autopsy after twenty hours in refrigerator. Kidneys found healthy. Stomach empty. The blood treated as just described yielded a gas bubble about 5·5 × 5·5 × 4 mm. The product of these multiplied by $\frac{1}{21}$ gives about 63 c.mm. as the volume of the gas bubble. Taking the yield of nitrogen from 1 grm. of urea, not as the usually accepted 380 c.c., but as 400 c.c. at 20° C., 63 c.mm. N would correspond to 0·016 per cent. of urea,

which would be the reading on a taper-ended tube graduated as a ureometer. But in the experiment $\frac{1}{8}$ c.c. of phosphomolybdic acid solution was added to 1 c.c. of preliminary centrifugate, which again was derived from only half that volume of blood. Therefore multiplying by $\frac{9}{8}$ and by 2 we get 0·036 per cent. of 'urea' in the blood. But urea, $CO(NH_2)_2$, contains nitrogen equal to $\frac{28}{60}$ of its weight. Accordingly the *filtrate nitrogen* in the blood is $\frac{7}{15}$ of 0·036, i. e. 0·017 per cent. The cerebro-spinal fluid treated similarly gave, as nearly as could be measured, the same percentage. This percentage is the lowest I have found in an adult. The taper-ended tube graduated as a *nitrometer* gives at once by its reading the percentage of nitrogen, requiring merely to be multiplied by such incidental factors as $\frac{9}{8}$ and 2, above.

In conclusion, I have acknowledgements to make: To Dr. Turnbull, for his keen interest and assistance; to Dr. Panton, for generously helping with facilities not otherwise available; and to the members of the staff and their housemen for specimens requiring a test; also, last but not least, to Dr. Percy Kidd and to Dr. Robert Hutchison, for the practical interest they have taken in the article.

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EXPERIMENTS WITH CHOLAEMIC RED CELLS AND NORMAL RED CELLS IN THE PRODUCTION OF A HAEMOLYTIC IMMUNE BODY IN THE RABBIT

By LEONARD S. DUDGEON

(From the Department of Pathology, St. Thomas's Hospital).

The red cells from a case of congenital cholaemia were subjected to various tests which will be referred to here.

The fragility of the patient's washed red cells which were employed for these experiments was tested in various strengths of sodium chloride in distilled water, and the control normal cells were tested in the same way.

Sodium Chloride Content of Test Fluid.	Cholaemic Cells.	Normal Human Cells.
0·35	Complete haemolysis	Complete haemolysis
0·40	,,	Distinct
0·45	,,	Faint trace
0·50	Incomplete haemolysis	None
0·55	Distinct	
0·60	,,	
0·65	,,	
0·70	Trace	
0·75	,,	
0·80	None	

The increased fragility corresponded to the fragility of sheep red cells, which are readily employed in the tissues of the rabbit so that an active haemolytic immune body is easily obtained, which is not so with normal human red cells. For this reason cholaemic red cells were employed for these experiments.

Both varieties of red cells were well washed in saline under sterile conditions and then prepared for injecting rabbits intravenously. The animals selected were similar in size and weight and were in good health. At the same time a control rabbit, also of similar weight, was used which was injected with sheep red cells prepared in the same way.

Three c.c. of washed and centrifugalized cholaemic red cells and control normal human red cells were suspended in sterile saline and then injected intravenously into the particular rabbits. The control rabbit was injected in the same way with the washed sheep cells and the same measured quantity was given.

Each rabbit was bled before the commencement of the inoculations so as to test the action of the sera on the particular red cells prior to the inoculations.

Ten days later the cholaemic patient was again bled from a vein as before, and also the control healthy man, and the inoculations were repeated, while at the same time the control rabbit was injected with sheep red cells.

All three rabbits were inoculated once a week with red cells until six injections had been employed.

Seven weeks from the commencement of the experiments each rabbit was bled from the axillary artery and the blood was collected aseptically in sterile bottles.

Final Result of the Examination of the Human Red Cell Rabbits (Cholaemic and Normal).

These rabbits were bled from the axillary artery at the end of the inoculation experiments, and the serum was heated in the usual way and then tested with guinea-pig complement and washed human red cells. Equal amounts of each were taken for these experiments, whether diluted or otherwise, and then incubated for an hour at 37° C. and the results recorded.

The results are shown in the accompanying table:

Rabbit.	Dilution of Immune Body. 0·5 c.c.	Complement. 0·5 c.c.		Red Cells (Human). 0·5 c.c.	Result.
Cholaemic	1 in 20	Undiluted	Pig	5 % normal	Complete haemolysis
,,	,,	,,	Human	,,	,,
,,	1 in 50	,,	Pig	,,	Incomplete haemolysis
,,	,,	,,	Human	,,	Trace
,,	1 in 100	,,	Pig	,,	,,
,,	,,	,,	Human	,,	None
Normal	1 in 20	,,	Pig	,,	Complete haemolysis in 10 minutes
,,	,,	,,	Human	,,	Complete haemolysis in 10 minutes
,,	1 in 50	,,	Pig	,,	Complete haemolysis in 10 minutes
,,	,,	,,	Human	,,	Complete haemolysis in 10 minutes
,,	1 in 100	,,	Pig	,,	Complete
,,	,,	,,	Human	,,	Incomplete
,,	1 in 500	,,	Pig	,,	None
,,	,,	,,	Human	,,	,,

Sheep red cell rabbit. Final examination of rabbit's blood obtained from the axillary artery. A 5 per cent. suspension of thoroughly washed sheep red cells were taken in saline, together with guinea-pig complement, and the rabbit's serum heated in the usual way. An equal quantity of each fraction was taken and the result recorded at the end of one hour at 37° C. The complement was diluted with saline as required and also the immune body.

The results are shown in the following table:

	Immune Body (Sheep Rabbit). 0·5 c.c.	Complement (Guinea-pig). 0·5 c.c.	Red Cells (Sheep). 0·5 c.c.	Result.
Dilution employed	1 in 50,000	1 in 10	5 %	Complete haemolysis
	1 in 100,000	,,	,,	Incomplete haemolysis
	1 in 1,000,000	,,	,,	Trace of haemolysis
	,,	Undiluted	,,	Complete haemolysis

Result of Post-mortem Examinations.

Each animal was quite healthy and had continued to gain in weight during the whole of the experiments, so that at the autopsies they were found to have a good covering of fat.

Nothing abnormal was noted at the post-mortem examinations on the rabbits, but the livers, kidneys, and spleens were taken for microscopical examination.

Microscopical Histology. Human and Cholaemic Red Cell Rabbits.

Livers. Both livers were found to contain a large amount of fat in the healthy looking liver cells, but in each case the appearances were similar. No free iron reactions were detected in either specimens.

Kidneys. Nothing abnormal was noted.

Spleens. In the case of both animals sections of the spleens showed very large number of eosinophils, both the mononuclear and the polynuclear types, and these cells certainly appeared to be in very large numbers even for splenic tissue in the rabbit. The sections also showed well-marked free iron granules, both intra- and extra-cellular.

Sheep Red Cell Rabbit.

Liver. Sections of this organ contained fine fat droplets all through the hepatic cells which appeared to be healthy.

Kidney. No fat and no free iron detected.

Spleen. Sections of this organ showed abundance of free iron all through the splenic tissue, both intra- and extra-cellular.

Weight of both Samples of Human Red Cells—Cholaemic and Normal.

0·5 c.c. of thoroughly washed red cells from the cholaemic cases and the normal control were dried over sulphuric acid in a vacuum chamber until of constant weight. The cholaemic red cells dried in this way were found to weigh 0·160 grm., and the normal red cells treated in the same way weighed 0·163 grm., a difference which can be readily explained as an experimental error.

A METHOD OF ESTIMATING THE 'VIBRATORY' SENSATION

By J. L. M. SYMNS

I. The History of the Investigation of the Vibratory Sensation

When the rays of the Sun, which arouse in the eye the sensation of light, strike the skin, they are only felt as warmth, not as light. So the movements of elastic bodies which the ear perceives may be felt by the skin, not as sound, but as vibration.—Helmholtz.

The history of the Vibratory Sensation began with a work by Rumpf (1). He collected a series of tuning-forks with vibrations varying from 13 to 1,000 per second, and investigated how different parts of the body responded to the various stimuli.

In 1895 Treitel (2), without any knowledge of Rumpf's investigations, conceived the idea of testing in the same way the sense of touch. He did not try, like Rumpf, to test the possibility of distinguishing varying amplitudes of vibration, but used one tuning-fork of 128 vibrations and examined with it the different parts of the body, finding how many seconds elapsed before the sensation ceased to be felt. This fork was 15 cm. long, and had a base of horn and at the end of each prong a movable clamp. Treitel took the time during which the vibrations were observed at different points of the body: skin of head, 8 seconds; skin of face, 7–8 seconds; skin of nose, 9–10 seconds; and finger-tips, 18–20 seconds. The vibrations are felt over the arms between 7 and 16 seconds, over the legs between 6 and 10 seconds.

The reason for these short periods is probably the fact that the fork was set in motion by pressing the two limbs together. This would give a small amplitude, which is borne out by the fact that the fork, when applied to the ear, could be heard only for 18 seconds. This method was illustrated by several cases, from which I quote the following verbatim:

Case I. Tabes dorsalis. Mr. M., 52 years old. Sensation of pain very marked on whole body, in palms of hands diminished. Sensation of touch in arms and back of hand well preserved, but diminished in palms of hands. Sensation of locality very slightly affected.

Duration of vibratory sensation:

Dorsum of hand and finger	5 seconds
Palmar surface of hands	5 „
Lower arm	2–3 „
Upper arm	4–5 „

Sensation of pain and touch lost in the legs, vibratory sensations also missing.

Case II. Alcoholic polyneuritis. Dr. ——, 61 years old. Sensation of pain in the upper extremities, except palms of hands, considerably diminished; the sensation of position much affected, but the lightest touch is felt at any place.

Duration of vibratory sensation:

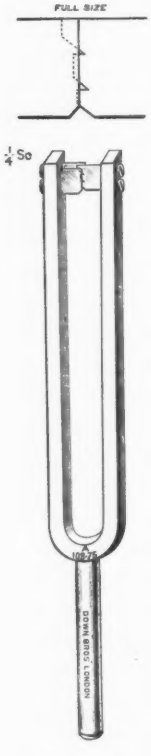
Palmar surface of hands	9–10 seconds
Dorsum of hands	11–12 „
Arm	4–6 „

In the leg the sensation of pain and touch is well preserved, but the vibratory sensation is reduced and lost in the

Right tibia, 4 seconds; left tibia, 2 seconds.

Right calf, absent; left calf, a moment.

He concluded that the sensation was distinct from that of touch, and that the vibrations of a tuning-fork would prove of value in estimating the condition of the sensory tracts.



R. T. Williamson (3) recommends a large tuning-fork; the one he uses is 7½ inches long and has an oval metal foot-piece. If the fork has no foot-piece, he recommends a coin being placed between the foot of the tuning-fork and the part tested. He advises the following points as suitable for testing: the styloid process of the ulna, the malleoli, the inner surface of the tibia, the sternum, the palms of the hands and soles of the feet, the nails of the fingers and big toes, and the anterior superior iliac spines.

This method adopted by Williamson is of great value in clinical work, but it does not show abnormal states which precede the total impairment of the sensation.

In my investigations, which date from 1911, and which were conducted without knowledge of Treitel's pioneer work, I used a tuning-fork obtained from Messrs. Down. Its vibration rate is 108·75. This is an excellent fork for use, as it is easily appreciated by the normal individual and is not too unwieldy for general use. Two pieces of steel are attached to the upper portion of the fork in such a manner that when the arms of the fork are vibrating, a small window is seen between them. This disappears when the vibrations of the fork reach a definite amplitude. At this moment, when the window disappears, I apply the fork to the subcutaneous bony point and start a stop-watch.

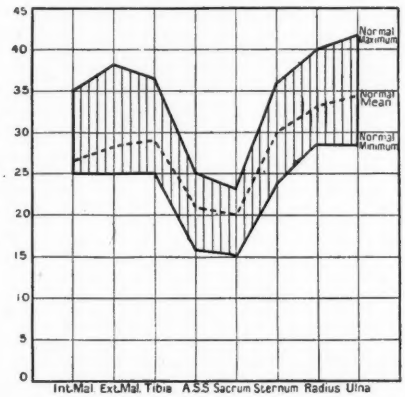
The patient is instructed to give a signal at the moment when he ceases to appreciate the vibration. The watch is then stopped and the time recorded. By this method the fork is always applied when it is vibrating at a definite amplitude. The subcutaneous bony parts taken are the internal malleolus, external malleolus, tibia, anterior superior spine of the ilium, sternum, radius, and ulna.

By this method, on thirty normal individuals between the ages of 18 to 30,

I found at each bony point what intervals of time elapsed before the sensation disappeared. The mean intervals, in seconds, together with the maximum and minimum for these thirty individuals, are shown in the following table:

	Mean.	Maximum.	Minimum.
Int. malleolus	27	35	25
Ext. malleolus	28	38	25
Tibia (middle of shaft, inner aspect)	29	37	25
Anterior superior spine of ilium	21	25	16
Sacrum	20	23	15
Sternum	30	36	24
Radius (lower end)	33	40	28
Ulna (lower end)	34	32	28

When this test is applied to patients suffering from impairment of the vibratory sensation, a numerical ratio to the mean normal is obtained which represents the degree of impairment of the sensation. This can be described graphically on the following diagram, the heights in which represent the time during which the sensation is appreciated by the normal individual.



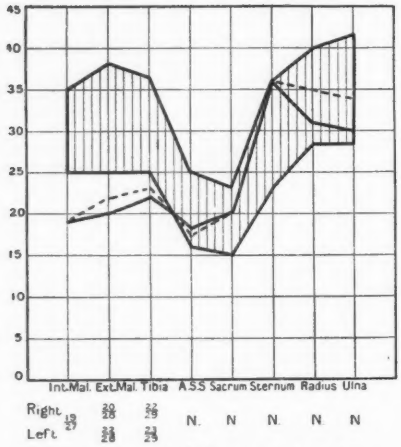
I have used this graphic method in this paper to show the abnormal state of the sensation in comparison with the normal.

Up to 1916 I was ignorant of Treitel's work on the subject, and as unknowingly I experimented with a similar fork with similar results, before adopting the method I now use, this paper would be incomplete without a short account of the difficulties which made me discard this fork for that made by Messrs. Down. (1) The length of time during which the sensation was appreciated was in pathological conditions too short to compare the sensation with the normal. (2) Many patients gave no response to the stimuli, but when tested with a fork of greater amplitude appreciated the sensation. (3) I was unable to devise any method by which the fork could be applied only while its arms were vibrating with a definite amplitude; consequently comparisons were not accurate. These difficulties I found were overcome by means of the tuning-fork made by Messrs. Down; and the greater amplitude made the sensation considerably easier for the patient to appreciate, and gave more accurate results.

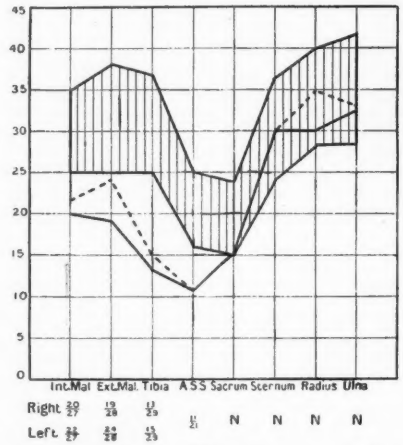
II. Clinical Cases.

A. *Peripheral Neuritis.*

I



II

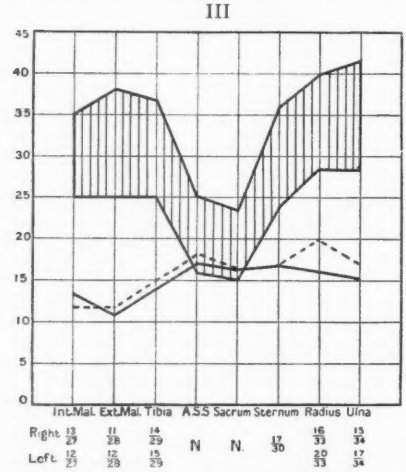


Case I. Diabetic peripheral neuritis. Male, aged 42. Wassermann reaction negative. Knee-jerks present when reinforced. Ankle-jerks absent. No sensory changes.

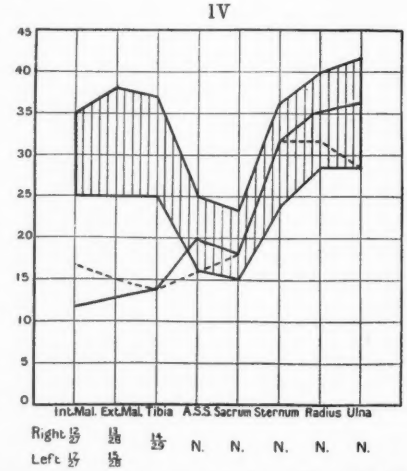
Case II. Diabetic peripheral neuritis. Male, aged 34. Knee-jerks absent. Ankle-jerks absent.

Sensations. Pain and cramp in muscles of calf on both sides. Hyperaesthesia over left leg from knee downwards.

III



IV



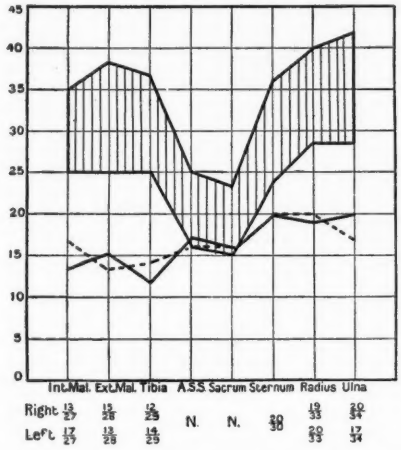
Case III. Diabetic peripheral neuritis. Male, aged 48. Knee-jerks absent. Ankle-jerks absent.

Sensations. Pain in arms, but no alteration in sensations. Hyperaesthesia over front and inner side of thigh on right side, hyperalgesia of the feet causing difficulty in walking.

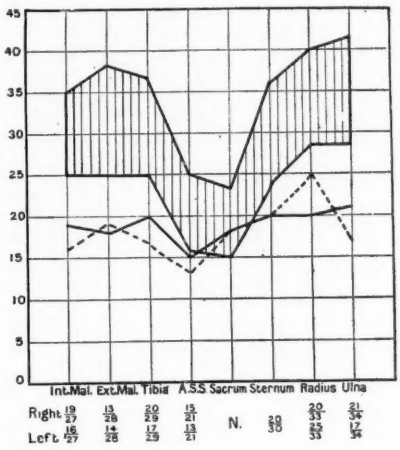
Case IV. Diabetic peripheral neuritis. Male, aged 51. Knee-jerks absent. Ankle-jerks absent.

Sensations. Numbness of lower limbs, but on examination there was no loss of tactile pain or temperature sensation.

V



VI



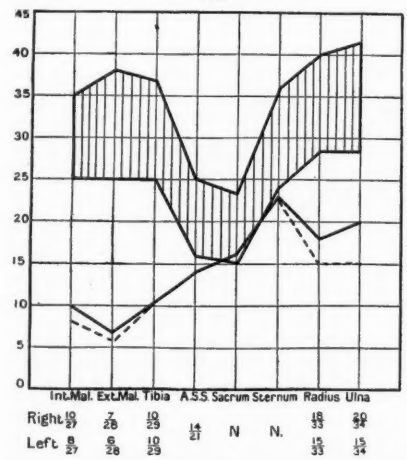
Case V. Alcoholic peripheral neuritis. Male, aged 37. Knee-jerks absent. Ankle-jerks absent.

Sensations. There was diminution in the temperature sensation over the left lower limb from the knee downwards; otherwise the sensations were normal.

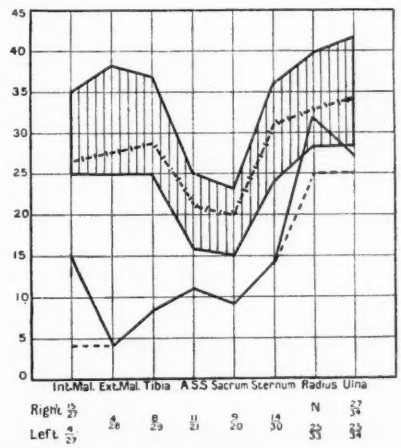
Case VI. Alcoholic peripheral neuritis. Male, aged 39. Wassermann reaction negative. Knee-jerks absent. Ankle-jerks absent. Marked tremor of hands.

Sensations. The sensations of pain, pressure, and temperature were normal, except on the dorsum of the right foot, where touch was not appreciated, but pain on pricking was very marked.

VII



VIII



Case VII. Alcoholic peripheral neuritis. Male, aged 37. Wassermann reaction negative. Knee-jerks absent. Ankle-jerks absent. Marked tremor of hands.

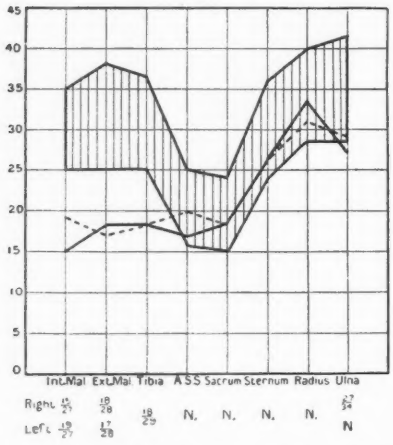
Sensations. Sensation of pain on the left foot and ankle was decreased, but sensations were otherwise normal.

Case VIII. Alcoholic peripheral neuritis. Female, aged 42. Wassermann reaction negative. Suffered from joint pains, headaches, and periodical vomitings.

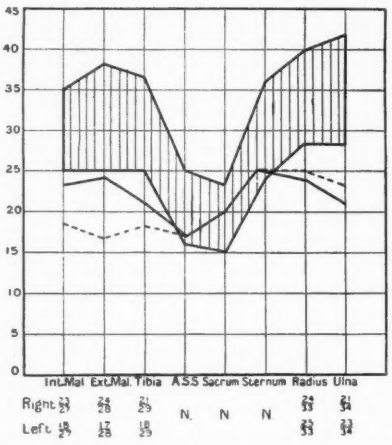
There was marked peroneal paralysis on both sides. The pain in her hands and arms was more excessive on the left than the right.

Knee-jerks and ankle-jerks were absent. Sensations of pain, temperature, and pressure were much reduced over the lower extremity, and those of deep pressure and localization were impaired over both lower extremities.

IX



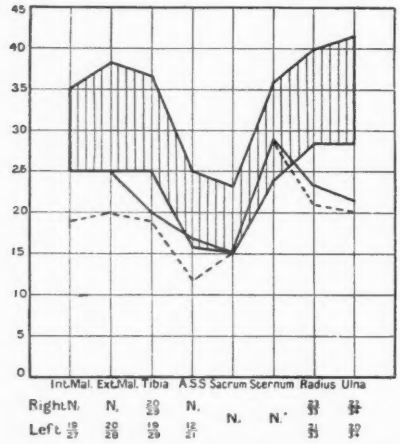
X



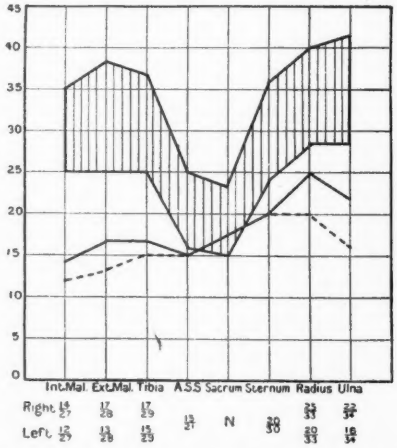
Case IX. Plumbic peripheral neuritis. Male, aged 53, who had worked in lead for thirty-four years. There was a slight blue line on gums. Knee-jerks present. Ankle-jerks present. No sensory changes.

Case X. Plumbic peripheral neuritis. Male, aged 29; painter for nine years. Right wrist-drop, blue line on gum. Knee-jerks present. Ankle-jerks present. No sensory changes.

XI



XII



Case XI. Plumbic peripheral neuritis. Male, aged 32, painter for eight years. Right wrist-drop, blue line on gum. Knee-jerks present. Ankle-jerks present. No sensory changes.

Case XII. Plumbic peripheral neuritis. Male, aged 43. Wassermann

reaction negative. Painter for twenty-one years. Blue line on gum. Knee-jerks absent. Ankle-jerks absent. No sensory changes.

I. *Diabetic neuritis.* The common sensory changes noticed in my cases have been pain, tenderness, and hyperaesthesia. These were all well marked in Case II. There was no loss of the tactile pain or temperature sensation in Case IV, although the patient complained of a feeling of numbness over the lower extremities.

In Case III the patient complained of pain and tenderness over the biceps on both arms, but there was no obvious alteration in the sensation. This case was remarkable for definite hyperaesthesia over the cutaneous area supplied by the anterior crural nerve; but there was no paralysis of the flexors and adductor of the thigh as in the similar case recorded by Buzzard in the *British Medical Journal*, 1890. In my case there was marked hyperalgia of the feet, which caused great difficulty in walking, and the patient at times complained of the pain caused by the weight of the bed-clothes.

The vibratory sensation in Cases I and II was diminished over the lower limbs, and this I have found to be typical of the twelve cases examined.

The sensation is always appreciated over the arms, except in the rare cases of neuritis of the upper limbs. Case XII shows this type of sensory defect, and the vibratory sensation was diminished over the arms. Clinically this patient had signs of a neuritis affecting both arms.

In my series the sensations of pain, temperature, and pressure were all present; but in all cases examined there was a diminution in the vibratory sensation, the time of appreciation of the vibrations of the tuning-fork varying from 5 to 20 seconds.

In none of these cases, with the exception of the one quoted above, was the vibratory sensation affected on the arms. The sensibility over the sternum was also normal in every case.

My observations have led me to conclude: (1) In diabetes mellitus the vibratory sensation is diminished, although other sensations are not. (2) This decrease affects the lower limbs only, except in cases of neuritis of the arms. (3) There is no decrease in the appreciation of vibration over the sacrum or anterior superior spine even in advanced cases. These facts are in agreement with Williamson (3), who states that often the only sensory defect in diabetic neuritis is a loss of the vibratory sensation over the feet and legs.

The fact that he found the sensation absent is, I think, due only to the amplitude of the fork used.

It is of interest to note in passing that Verneuil had drawn attention to the rule that in cases of fractures in diabetics the ends of the bones are remarkably insensitive (4).

II. *Alcoholic peripheral neuritis.* In the cases of alcoholic neuritis that I have examined, the sensory changes other than the vibrating sensation have been indefinite. In Case VIII the sensations of pain, temperature, and pressure were

reduced over the lower limbs. In Case VII the sensation of pain was decreased over the left foot and ankle, but other sensations appeared normal. The only abnormality in sensation in Case V was a diminution in the temperature sensation, from the knee downwards, on the left side. These three cases were typical of the sensory changes in ten cases examined. The most consistent change was a diminution of the sensation of pain over varying areas of the lower limbs in five cases.

Case VI presented a condition described by Oppenheim (5) and considered by him to be almost pathognomonic. The sensations of pain, pressure, and temperature were normal, except on the dorsum of the right foot, where touch was not appreciated; but there was very marked hyperalgia on pinching. In contrast to these very indefinite sensory changes, the vibratory sensation was in every case diminished over the legs and arms.

The appreciation of the vibrations was normal over the sacrum and anterior spines until an advanced stage in the disease (Case V). In seven cases out of the ten the diminution on the right and left side varied only by a few seconds (between 1 and 8), confirming the fact that the neuritis is due to a systemic poisoning. In marked difference between the vibratory sensation in diabetic neuritis, the arms were always affected and the sacrum in advanced cases.

To sum up: (1) In alcoholic neuritis the vibratory sensation is diminished, although otherwise sensation may be clinically normal. (2) This decrease involves the upper and lower limbs. (3) In advanced cases the vibratory sensation is diminished over the anterior superior spines and sacrum.

III. *Plumbic neuritis.* In the eight cases examined the sensations of pain, pressure, and temperature appeared normal. In all cases the vibratory sensation was diminished at some point. The lower limbs showed the diminution in sensibility in every case; the arms were affected in six cases and in two the legs were affected alone. In the two cases of wrist-drop the vibratory sensation was subnormal over both arms.

The vibratory sensation in the three types of neuritis can now be summarized. In plumbic neuritis, as contrasted with the diabetic and alcoholic types, there does not seem to be the same constancy in the manner of distribution of the vibratory sensation. In diabetic neuritis it is diminished over the legs. In alcoholic neuritis the vibratory sensation is diminished over the arms and legs, but in plumbism, although we get the same area of diminution in the majority of cases, in a certain number the sensation is diminished only over the lower limbs. This comparison I show in the attached table. There is one point, however, common to all three, and which I have found constant in all cases of neuritis, namely, until a late stage in the disease the vibrations are appreciated normally over the sacrum.

There appears to be no connexion between the diminution in the vibratory sensation and that of the other sensations. In Case V there was a general depression of the sensations, including those of the 'deep system'. I can only

conclude that the ordinary clinical methods of estimating them are not delicate enough to show the slightest degrees of impairment.

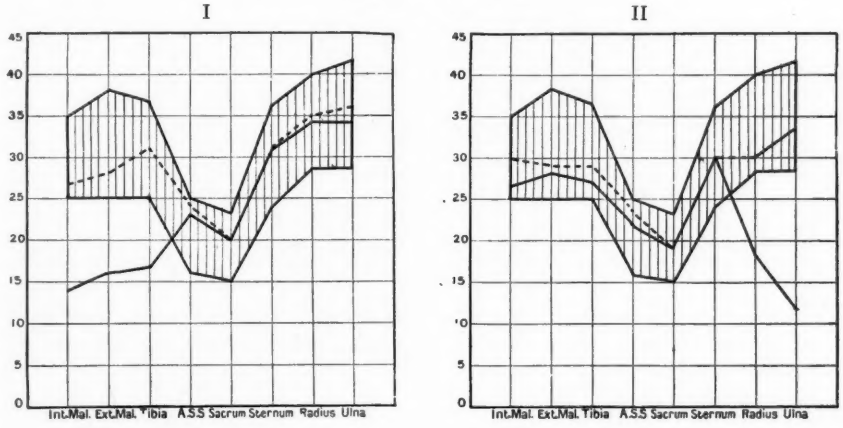
The examination of the vibratory sensation by this method has the great advantage over that of other sensations in that its diminution as distinct from total loss can be measured. It can also be rapidly tested, and the elements of fatigue and suggestion, which play so large a part in the examination of other sensations, are avoided.

A Table showing the Typical Appreciation of Vibratory Stimuli in Case of Diabetic, Alcoholic, and Plumbic Neuritis.

N denotes Normal, and — a diminution in the sensation.

Area noted.	Diabetic Neuritis.	Alcoholic Neuritis.	Plumbic Neuritis.
Arm	N	—	— (not invariably)
Sternum	N	N	N
Sacrum	N	— in advanced case	N
Legs	—	—	—

B. *Cases of Injury to Nerves.*



Case I. Fracture left femur; left sciatic nerve implicated in callus with injury to external popliteal fibres. Loss of sensation to prick, fine touch, heat and cold, over dorsum of left foot.

Vibratory sensation:

Left internal malleolus . . . . . $\frac{14}{27}$ N.
Left external malleolus . . . . . $\frac{16}{28}$ N.
Left tibia . . . . . $\frac{17}{29}$ N.

Case II. Sutured ulnar nerve (October 1916). Some wasting of themar and hypothemar eminences, but none of interossei. Loss of all sensations over little and ulnar side of ring finger.

Vibratory sensation:

Right radius . . . . . $\frac{18}{33}$ N.
Right ulna . . . . . $\frac{13}{34}$ N.

Case III. Injury to right median and ulnar nerves. Adductor pollicis very weak. Wasting of forearm and hand; also biceps and triceps; some contraction of flexor. Sensations right hand (dorsal surface): Terminal phalanx of thumb showed loss of sensation to prick and fine touch, and to hot and cold tubes; also terminal phalanges of first and second digits. There was dullness to pin-pricks, but no loss to fine touch on the rest of the thumb and first and second digits. This condition was also present on the third and fourth digits. Palmar surface: There was loss of prick and fine touch over all the digits; thermal sensation present but deficient.

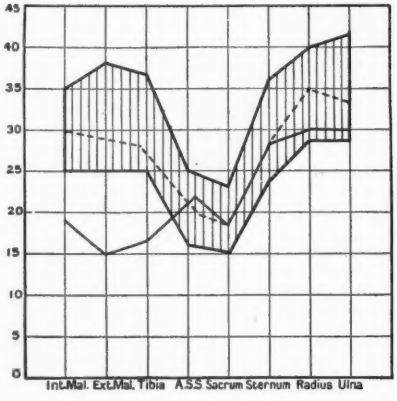
Vibratory sensation:

Right radius . . . . . $\frac{2}{33}$ N.
Right ulna . . . . . $\frac{2}{34}$ N.

III



IV



Case IV. Shrapnel wound causing injury to external and internal divisions of right sciatic nerve. When seen he had been under treatment for four months, and was much improved. Muscles:

Tibialis anticus .
Peroneus longus . } reacted nil to faradic and slightly to galvanic.
Gastrocnemius .

His right foot was sweating, but his sensations of pain, temperature, and pressure were normal.

Vibratory sensation:

Right internal malleolus . . . . . $\frac{19}{27}$ N.
Right external malleolus . . . . . $\frac{15}{28}$ N.
Right tibia . . . . . $\frac{17}{29}$ N.

Case V. Paralysis of posterior interosseous nerve. Fell on the left arm, three weeks previously, followed by loss of movement of left hand. When seen could lift wrist to the horizontal, but no farther. Could turn wrist to the radial side, but not to the ulnar. Cannot extend finger at metacarpo-pharyngeal joints or abduct thumb.

Muscles:

Extensor carpi radialis Supinator longus	act readily to faradic.
Extensor communis digitorum Extensor carpi ulnaris Extensor pollicis	act nil to faradic, but fairly well to galvanic.

Sensory changes: nil.
Vibratory sensation: normal.

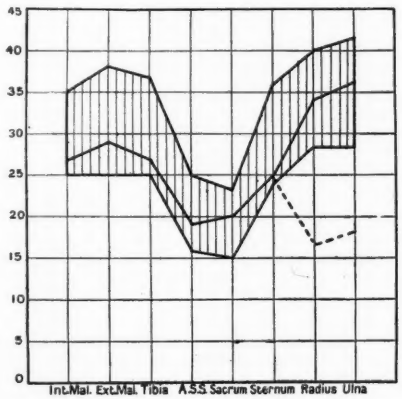
Case VI. Fell three weeks previously, bruising his forearm. When seen had injury to radial nerve.

Sensations: Dull to pin-pricks and pressure over radial area of hand; hot and cold sensations were mixed over that area.

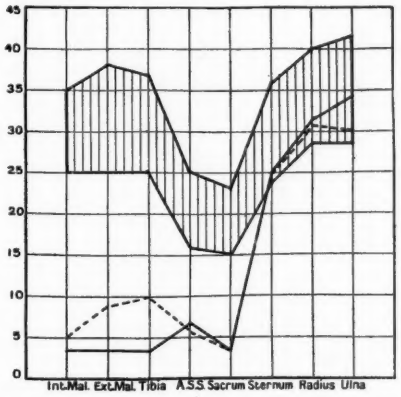
Vibratory sensation:

Left radius . . . . . $\frac{17}{33}$ N.
Left ulna . . . . . $\frac{17}{34}$ N.

VI



VII



Case VII. Bullet wound of spine between sixth and seventh dorsal vertebrae. Could flex both legs at hip and knee, but had difficulty in extending them. Very slight wasting of leg muscles. Some contraction of flexors and abductors. Patellar clonus, ankle clonus, and extensor plantar reflex on both sides.

Sensations on body from two inches below nipples. Sensation to pin-prick a little impaired. Could locate fine touch fairly well. Could differentiate hot and cold tubes. Could not judge size of objects with which he was pressed. Compass test very imperfect, but correct to 3 cm. on dorsum of feet.

Vibratory sensation:

Right internal malleolus . . . . . $\frac{3}{27}$ N.
Right external malleolus . . . . . $\frac{3}{28}$ N.
Right tibia . . . . . $\frac{3}{29}$ N.
Right anterior superior spine . . . . . $\frac{7}{21}$ N.
Sacrum . . . . . $\frac{3}{20}$ N.
Left internal malleolus . . . . . $\frac{5}{27}$ N.
Left external malleolus . . . . . $\frac{9}{27}$ N.
Left tibia . . . . . $\frac{10}{29}$ N.
Left anterior superior spine . . . . . $\frac{6}{21}$ N.

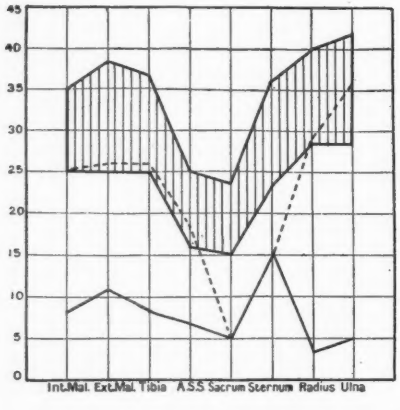
Case VIII. Shrapnel wound, left parietal region, 20 cm. from gabella and 5 cm. to left of mid-line, on August 1, 1916. Right hemiplegia, after six or seven weeks could use his right arm; could walk in four weeks. Leg was always much less affected than arm. No history of facial paralysis.

Loss of touch over whole of right arm. Pain sensation dull over the same area. Pressure sensation less distinct than on left arm. Temperature sensation dull, but can detect moderate temperature fairly well. Legs and body appear normal. Patellar clonus. Extensor plantar reflex right side.

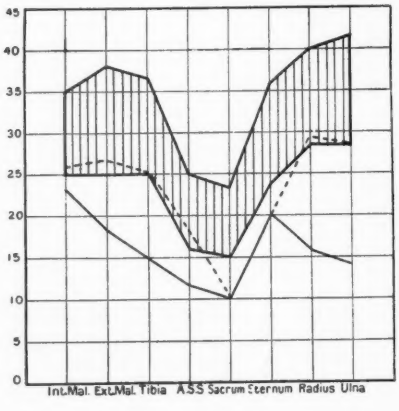
Vibratory sensation:

Right internal malleolus	$\frac{8}{27}$ N.
Right external malleolus	$\frac{11}{28}$ N.
Right tibia	$\frac{8}{29}$ N.
Right anterior superior spine	$\frac{7}{21}$ N.
Sacrum	$\frac{5}{20}$ N.
Sternum	$\frac{15}{30}$ N.
Right radius	$\frac{3}{33}$ N.
Right ulna	$\frac{5}{34}$ N.

VIII



IX



Case IX. Shrapnel wound of head, April 12, 1916. Scar 6½ in. above gabella and 1½ in. to right of mid-line. No wasting of limbs. Limitation of movements on left side, signs of facial paralysis. Ankle clonus, increased knee-jerk, and extensor plantar reflex on left side.

Sensations: No alterations of sensations of heat, cold, pressure, pain, or temperature.

Vibratory sensation:

Left internal malleolus	$\frac{23}{29}$ N.
Left external malleolus	$\frac{18}{28}$ N.
Left tibia	$\frac{15}{29}$ N.
Left anterior superior spine	$\frac{12}{21}$ N.
Sacrum	$\frac{16}{20}$ N.
Sternum	$\frac{26}{20}$ N.
Left radius	$\frac{16}{33}$ N.
Left ulna	$\frac{14}{34}$ N.

Case X. Gunshot wound of right arm involving brachial plexus. Musculo-spiral and ulna completely divided; musculo-cutaneous and median incomplete.

Flexor group . .	No response to faradic; slight to galvanic.
Extensor . . .	Nil to faradic; slight to galvanic.
Supinator longus .	Nil to faradic; good to galvanic.
Triceps . . .	Nil to faradic; fair to galvanic.
Interossei . . .	Nil to faradic; slight to galvanic.

Sensations: *Hand* and *wrist.*

Dorsal surface.

Loss of fine touch. Two terminal phalanges of first finger, base of second finger, and terminal phalanx of thumb.

Loss of prick, fine touch, and deep pressure. Rest of dorsum of hand and wrist, little finger, third phalanx of first finger, and base of third finger.

Heat and cold. Indefinite over hand and wrist.

Palmar surface.

Loss of fine touch. Thumb and first finger, continuing to wrist.

Loss of prick, fine touch, and deep pressure. Fourth finger, radial side of third finger, continuing to wrist.

Heat and cold. Indefinite over hand and wrist.

Vibratory sensation:

Right radius . . . . . $\frac{15}{33}$ N.

Right ulna . . . . . $\frac{12}{34}$ N.

Right olecranon, 12 sec.; left olecranon, 28 sec.

Right external condyle, 14 sec.; left external condyle, 28 sec.

Right internal condyle, 15 sec.; left internal condyle, 29 sec.

On the next page I have tabulated the chief facts relating to the nine cases of nerve injury. The following results will be noted: (1) The diminution in the vibratory sensation was not associated with diminution of any other sensation. (2) After an injury, when the sensory paths have recovered and appear normal, the vibratory sensation may still be impaired. (3) When both sides of the body are affected, although loss of sensation may seem equal on the two sides, the vibratory sensation may show a considerable difference between them, pointing to the fact that the lesions are due to local causes and not to systemic poisoning.

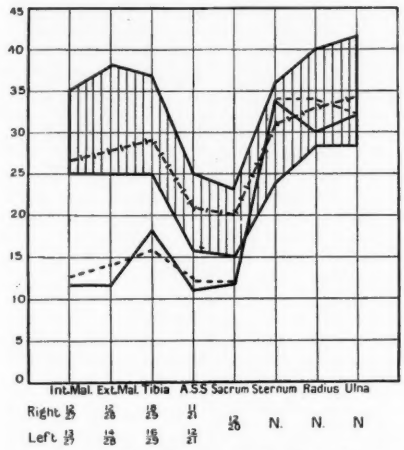
Consequently we must conclude that the vibratory sensation can be utilized to show slight impairments of sensation; but clinically it cannot be correlated in any way with impairment of other sensations. We cannot compare the stimulation of a tuning-fork to the touch of a von Frey's hair or the prick of a needle. One is the summation of stimuli transmitted to an indefinite area around, and the other a single stimulus applied to a point.

I shall return to this subject in Part IV, as it is of great importance; until the nature of the sensation is accurately known all comparisons with other forms of sensation are extremely difficult. I am indebted to Col. J. Griffith, Officer in charge 1st Eastern General Hospital, and Dr. L. E. Shore, of Cambridge, for allowing me to examine these cases of nerve injuries, and to the latter for allowing me to make use of his notes.

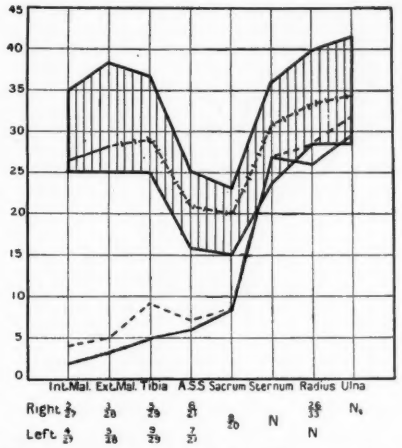
Table showing Summary of Cases of Injury to Nerves.

Case.	Injury.	Conditions of Sensations other than Vibratory.	Area.	Condition of Vibratory Sensation, Approximate.	Area.
I.	Ext. popliteal nerve	Loss of— Prick Fine touch Thermal	Dorsum of foot	50 % reduction	Malleoli and tibia
II.	Old injury to ext. and int. division of sciatic nerve	Normal	—	40 % reduction	Malleoli and tibia
III.	Median and ulnar nerves	Diminution of— Prick Fine touch Thermal	Over fingers	94 % reduction	Radius and ulna
IV.	Ulnar nerve	Loss of all	On little finger and ulnar side of ring finger	45 % reduction	Radius and ulna
V.	Posterior interosseous nerve	Normal	—	Normal	
VI.	Radial nerve	Diminished— Prick Thermal	Radial area of hand	50 % reduction	Radius and ulna
VII.	Spine 6–7 Dorsal	Diminished— All	2 inches below nipple downwards	60 % reduction 20 % reduction	Right side of body Left side of body
VIII.	Left parietal region	Loss of touch Diminished— Pain Pressure Thermal	Right arm Right arm	75 % reduction	Right side of body
IX.	Right parietal region	Normal	—	50 % reduction	Left side of body

I



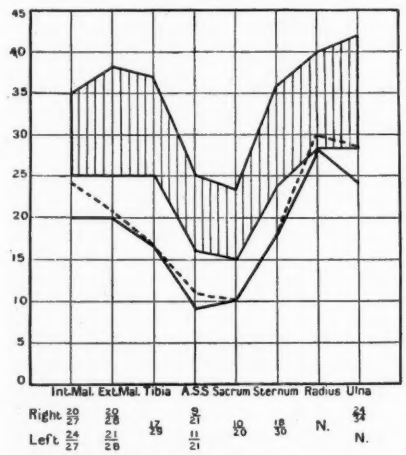
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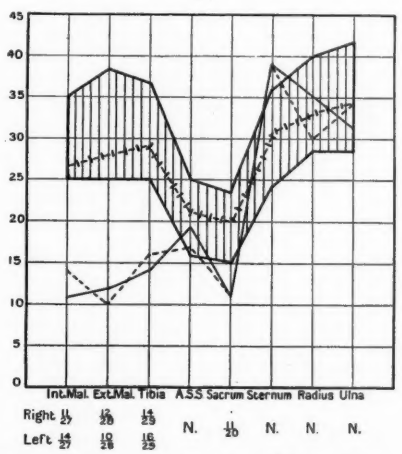
Case I. Male, aged 45. Chancre fifteen years previously, Wassermann reaction positive. Frequency of micturition, for five months constipated. Pupils Argyll Robertson. Ocular muscles, slight double ptosis. Knee-jerks and ankle-jerks absent. Romberg's sign present but not marked. No ulnar analgesia. Sensations of touch and deep pressure normal.

Case II. Male, aged 37. Chancre seven years previously. Wassermann reaction positive. Pupils react to accommodation, slow to light, unequal. Knee-jerks and ankle-jerks absent. Romberg's sign well marked. Sensation of deep pressure and of position was very deficient in the lower limbs. Sensation of touch was diminished over small area of both legs.

III



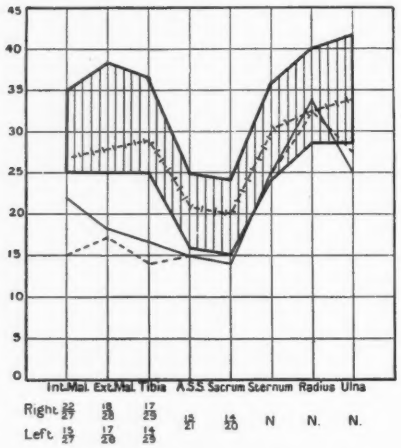
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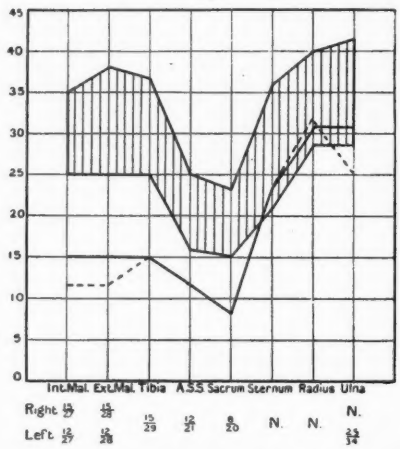
Case III. Male, aged 50. Chancre twenty years previously. Wassermann reaction partial positive. Retention and then difficulty in micturition. Pupils equal, react sluggishly to light, normal to accommodation. Slight left lateral nystagmus. Knee-jerks and ankle-jerks absent. Marked ulnar anaesthesia. Romberg's sign very slight. Sensations of touch and deep pressure normal.

Case IV. Male, aged 42. Wassermann reaction positive. Pupils Argyll Robertson, right larger than left. Right knee-jerk absent, left present. Both ankle-jerks absent. Ulnar anaesthesia. Romberg's sign marked. Sensations of touch and deep pressure normal.

V



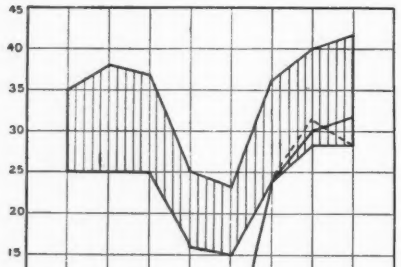
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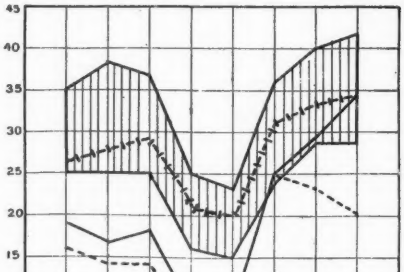
Case V. Male, aged 60. Wassermann reaction positive. Gastric crises. Frequency of micturition. Knee-jerks and ankle-jerks absent. Romberg's sign slight. Sensations of touch and pressure normal.

Case VI. Male, aged 42. Wassermann reaction positive. Argyll Robertson pupils. Frequency of micturition. Knee-jerks present when reinforced. Ankle-jerks absent. Romberg's sign slight. Sensations of touch and pressure normal.

VII



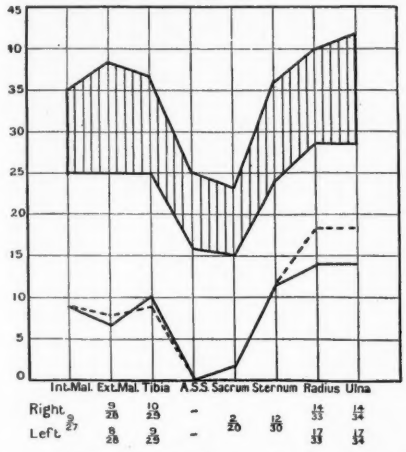
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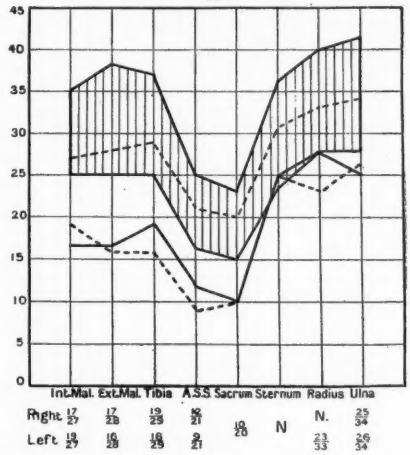
Case VII. Male, aged 37. Chancre ten years previously. Wassermann reaction positive. Pupils Argyll Robertson. Frequent and painful micturition. Knee-jerks and ankle-jerks absent. Romberg's sign very marked. There was marked diminution in deep pressure over the limbs and lack of localization. The sensation of touch was diminished over the dorsum of the right foot.

Case VIII. Male, aged 43. No history of syphilis. Wassermann reaction positive. Pupils Argyll Robertson. Knee-jerks and ankle-jerks absent. Difficulty in micturition. Romberg's sign slight. Sensations of pressure and touch appeared normal.

IX



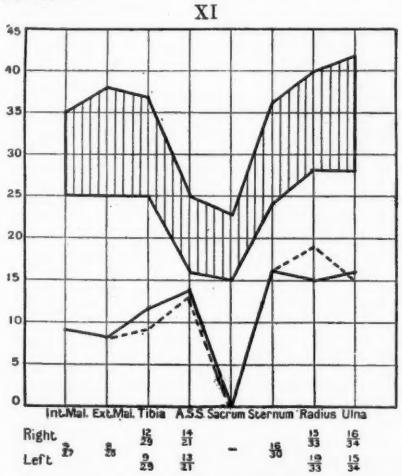
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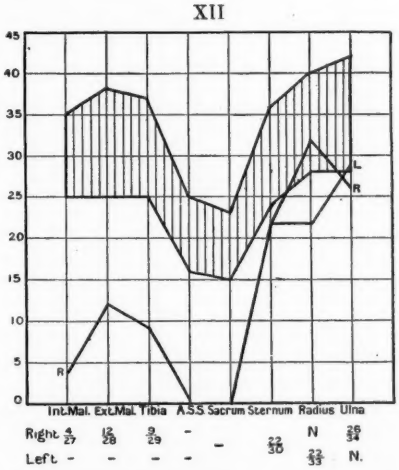
Case IX. Male, aged 45. Syphilis twenty years previously. Wassermann reaction positive. Pupils Argyll Robertson. No trouble in micturition. Knee-jerks present when reinforced. Ankle-jerks absent. Loss of power in arms. Romberg's sign marked. There was some diminution in the sensation of deep pressure over the legs and diminished power of localizing the position of arms and legs. I could find no diminution in the sensation of touch.

Case X. Male, aged 33. Syphilis eight years previously. Pupils Argyll Robertson. Vesical pains during micturition. Knee-jerks absent. Ankle-jerks absent. Romberg's sign very slight. Sensations of pressure and touch appeared normal.

XI



XII

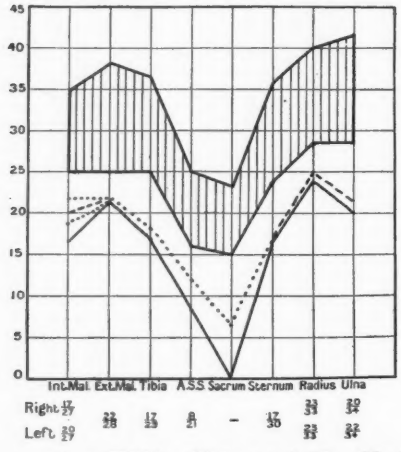


Case XI. Male, aged 34. Chancre eight years previously. Wassermann reaction positive. Pupils Argyll Robertson. No trouble in micturition. Knee-jerks present but slight. Ankle-jerks absent. Romberg's sign marked. There was some diminution in deep pressure over the legs, and some difficulty in localizing position of legs. Touch was normal.

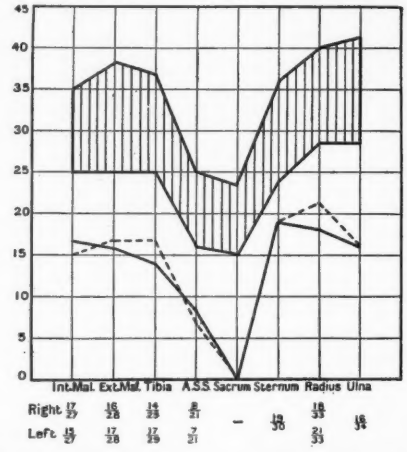
Case XII. Male, aged 45. No history of syphilis. Wassermann reaction positive. Pupils Argyll Robertson. Pain and difficulty in micturition. Knee-

jerks absent. Ankle-jerks absent. Romberg's sign marked. Deep pressure sensation was much impaired over the legs, but touch was only impaired over the left calf.

XIII



XIV

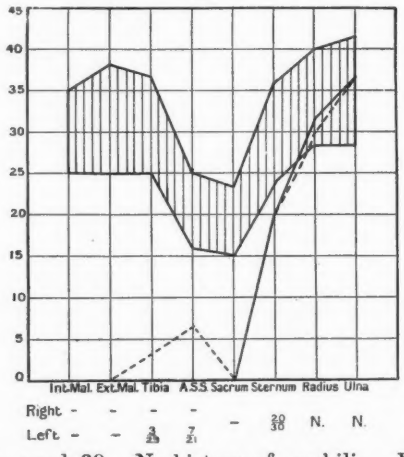


Case XIII. Male, aged 50. No history of syphilis. Wassermann reaction positive. Pupils irregular, Argyll Robertson. Knee-jerks present. Ankle-jerks absent. Romberg's sign slight. Sensations of pressure and touch appeared normal.

A year later the knee-jerks had disappeared, and the vibratory sensation had diminished, as shown in the diagram.

Case XIV. Male, aged 43. Syphilis sixteen years previously. Wassermann reaction partial positive. Pain during micturition. Pupils Argyll Robertson. Knee-jerks and ankle-jerks absent. Romberg's sign slight. Sensations of pressure and touch appeared normal.

XV



Case XV. Male aged 39. No history of syphilis. Wassermann reaction positive. Pupils Argyll Robertson. Knee-jerks absent. Ankle-jerks absent. Romberg's sign very marked. The deep sensation was very deficient over the lower limbs; sensation of position was also very limited.

Treitel, in 1897 (2), had shown that there was diminution in the vibratory sensation in tabes dorsalis. In a case recorded by him, quoted previously in this paper, he noted that the vibratory sensation was very much diminished over the legs, although the sensation of pressure was normal. In all his cases of tabes (4) there was a similar deviation from the normal. He concluded that the sensation of touch was not always affected to the same degree as the vibratory sensation, and conversely.

R. T. Williamson (3), writing in 1911, noted that in cases of tabes the vibratory sensation is lost on the legs, though other forms of sensation may be normal. This writer also agrees with Mott that in these cases the vibratory sensation, although present at other points, may be absent over the sacrum.

The charts which I have made showing the condition of the vibratory sensation in cases of tabes confirm and extend this observation of Treitel and Williamson. (1) In cases of tabes the vibratory sensation is deficient over the lower limbs and sacrum. (2) The arms may be affected, and this may be accompanied by a deficiency in the sensation of position. (3) The loss of sensation is equal over the two limbs. (4) In six cases there was a definite lowering of the deep pressure sensation and of that of position. In these cases the vibratory sensation was exceptionally deficient, and Romberg's sign was very well marked. (5) The amount of Rombergism present was parallel to loss of the power of appreciating the vibrations (see p. 57). (6) The vibratory sensation is always decreased over the sacrum in contrast to the condition of the sensation in all forms of peripheral neuritis, in which conditions the sensation is not decreased over the sacrum until a late stage in the disease.

I did not examine these cases with a view to recording the state of the cutaneous sensibility, with the exception of touch, but in six cases there was a distinct diminution in the sensations of deep pressure and position, and in these cases the degree of Rombergism appear to be affected in proportion to the decrease of these sensations, as also of the vibratory sensation.

D. *Disseminated Sclerosis, &c.*

I have found that in cases of amyotrophic lateral sclerosis, progressive muscular atrophy, and paralysis agitans, the vibratory sensation is normal.

In disseminated sclerosis there was a diminution in the vibratory sensation over the sacrum in all cases (6), but the diminution over the limbs was not constant. Two cases both lower limbs and right arm. Two cases right lower limb and left arm. Two cases left lower limb and right arm.

In cases of sciatica I have always found a diminution over the affected side, and in one case in which the neuritis was associated with diabetes the depreciation of the sensation was noted over both legs, but was 10 per cent. less on the side of the neuritis.

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III. The Diagnostic Value of Diminution of the 'Vibratory Sensation.

I have shown in Part II of this paper the condition of the vibratory sensation in cases in which the clinical diagnosis was clear, and I would call attention to the following points: (1) When the vibratory sensation is diminished over the sacrum, the disease involves the spinal cord. (2) When the vibratory sensation is impaired over one or other extremity the disease involves the peripheral nerves only. (3) If the diminution of the vibratory sensation is general we are dealing with a systemic poisoning. (4) If the diminution is unilateral we are dealing with a localized lesion of the nervous system.

In cases in which chronic alcoholism is suggested, and in which the ankle-jerks are still present, the vibratory sensation will often be found to be diminished over the limbs; if such a case is followed, later the ankle-jerks will disappear, making the diagnosis certain.

I have discussed the difference between the types of neuritis earlier in this paper, but the vibratory sensation may be of great value in differentiating peripheral neuritis from other diseases. R. T. Williamson (3) uses this sensation in the differential diagnosis of peripheral neuritis and acute anterior poliomyelitis of adults. He quotes a case of total paralysis of all four limbs after an attack of influenza in which suspicion of acute anterior poliomyelitis was raised. The symptoms were chiefly motor paralysis, with loss of knee-jerks and tendo Achillis reflexes. Bladder and rectum were not affected. The muscles of the calves and arms were tender on pressure, sensation for tactile impression was not lost, but the vibratory sensation on the leg was absent. This last symptom was in favour of peripheral neuritis, and the clinical course and complete recovery after many months indicated that this diagnosis was correct.

Again, in cases of sciatica the vibratory sensation will be found to be diminished over the affected limb and aids the diagnosis.

I have seen several cases of very early tabes in which the only signs were Argyll Robertson pupils, absent ankle-jerks, and a positive Wassermann reaction; all of these cases showed a diminution of the vibratory sensation over the lower limbs and sacrum.

In conclusion, I would again point out that in all diseases in which there is impairment in sensation, the vibratory sensation will be found impaired, and by this method the impairment will be noted before the loss of other sensations can be detected.

IV. The Nature of Vibratory Sensation.

Rumpf (1), in 1889, writing in the *Neurologisches Centralblatt*, called attention to the stimuli of a tuning-fork when applied to cutaneous surfaces; he concluded that the sensation was transmitted by the cutaneous nerves, as in the case of the sensations of heat, cold, and pressure. Egger (6), in 1897, named this sensation 'la sensibilité osseuse'. He considered that the periosteum, the ligaments, and the capsules of the joints were the anatomical basis of the sensation.

He stated that the nerve impulses that gave rise to the sensation took place at the point of contact, on the grounds that: (1) On the long bones there are islands of anaesthesic bone as well as normal sensitive areas. (2) In organic hemianaesthesia, the vibrations of the fork were not noted over the sternum on the anaesthetic side, but were noted on the opposite side.

This first statement I have been unable to verify, and in my cases of organic hemianaesthesia the sensation of vibration was felt on both sides of the sternum. R. T. Williamson (3) agrees with this and states: 'In hemianaesthesia, if the vibrating feeling is lost when the tuning-fork is placed on the lateral edge of the sternum on the side of the tactile anaesthesia but felt when placed on the other lateral edge of the sternum, in my opinion the case is probably one of hysterical or functional hemianaesthesia or malingering. In hemianaesthesia due to organic disease . . . the vibrating sensation is felt when the foot of the tuning-fork is placed on both lateral edges of the sternum.'

Treitel (2), in 1897, found that there was very slight difference in the appreciation of the sensation over the tibia and the soft parts of the gastrocnemius, and considered that the vibratory sensation had its origin not in the nerves of the periosteum but in those of the skin and soft structures. His belief was strengthened by finding that vibrations were appreciated over soft parts that had no immediate foundation of bone.

Up to this point we are faced with considerable differences of opinion, and there are few facts to support an hypothesis either of bone or skin sensibility to the vibratory stimuli.

In 1904 Minor of Moscow (7) took up the question, and in a series of experiments on subjects suffering from bone lesions showed: (1) The continuity of bone is not essential to the existence of a normal sensation of vibration. Even in the case of a severe fracture associated with splintering or dislocation of a neighbouring joint, the sensation remains normal. (2) The vibrations of a tuning-fork are appreciated normally on bone limited at one end by a fracture and at the other by a damaged joint. (3) Periostitis, caries, and superficial thickening of bone exercise no influence on the vibratory sensation. (4) The vibrations are plainly felt if the vibrating fork is placed on bared bones, with or without periosteum, or sequestra. (5) In cases where, in addition to the

bone, the peripheral nerve is injured there is usually a loss of the vibratory sensation.

These conclusions of Minor agree with the following cases noted by me:

Case I. A man, aged 38, suffering from a fractured tibia at the junction of the middle and lower third. The vibrations of the tuning-fork were appreciated for the normal period above and below the site of the fracture.

Case II. A man, aged 21, with a compound fracture involving the middle third of the femur. He appreciated the sensation for 26 seconds, although the fork was applied to a large loose sequestrum. On the femur on the normal side his time of appreciation was 29 seconds.

Case III. A man, aged 23, suffering from a fractured femur, had considerable oedema and swelling following a bone-plating operation. His appreciation of the sensation was one-half normal over the oedematous tissue.

This case is of considerable interest in showing the part played by the soft structures in the conduction of the sensation. The physical constitution of the tissues seems to be of great importance. The tuning-fork sets the skin and tissues beneath vibrating, and by this means stimulation of the nerves is obtained. Goldscheider (8) has shown that where the skin is soft and yielding the vibrations are not so clear as when it is taut and elastic; consequently, although the tongue is very sensitive to touch, it appreciated the sensation of vibration badly.

Bones, on account of their firmness and elasticity, take up the vibrations and transmit them to neighbouring structures.

I have earlier in this paper drawn attention to the diminution in the appreciation of vibrations felt when the peripheral nerves are injured, and it can now be stated that: (1) No definite part can be ascribed to the joints as indispensable between the stations for the conduction of the vibratory sensation. (2) Lack of continuity of bony structures, either by fracture or pathological changes in the joint, has no effect on the transmission of the sensation. (3) Injury to peripheral nerves is accompanied by a diminution in the appreciation of the sensation. (4) It seems probable that the vibratory stimuli are transmitted to the skin and soft parts, and thence are conducted as are the other sensations. The analogy of the vibratory sensation to other sensations cannot at present be carried farther.

The stimulus is not limited to the point of application, as in the case of other sensations, but is transmitted to a variable area around. This is clearly shown if the hand be laid on the knee and a vibrating tuning-fork applied to the hand. The vibration will be distinctly transmitted to the knee.

The stimulus is also applied continuously in testing, in contrast to our methods of testing tactile pain or thermal sensation in which the stimulus is momentary. It has long been noted that in a person who does not respond to a pin-prick, sensation may be obtained by drawing the pin along the skin. This is attributed by Egger (6) to a summation of stimulations. Now in the vibrations of a tuning-fork we make not a single application of a stimulus but

a succession of rapidly applied stimuli; and I have often found that a tuning-fork of a certain amplitude will be perceived where one of lesser amplitude calls forth no response. This contrast has been observed by many writers. It does not seem difficult, therefore, to suppose that one beat of a tuning-fork, an impression comparable to a stimulus by a pin-prick or a von Frey's hair, would not be appreciated, although a succession would be noted. It follows that it is theoretically sound to resolve the stimuli of a vibrating tuning-fork into a summation of pressure stimuli which, owing to the intensity of the summation, are taken up by the superficial nerves, and also by those of the deeper structures. This supposition will agree with all the cases noted above, and will justify us in resisting the assumption that there must be a new and independent sensory faculty for every new instrument employed in testing sensations.

We are now in a position to analyse the sensation of pressure, and to see if it corresponds with the sensation noted when the vibrating tuning-fork is applied. In the experiments of Rivers and Head it was shown that if the cutaneous nerves to any part were divided without injury to the motor trunk, all stimuli that produce deformation of structure are still perceived, but there is loss of all epicritic sensibility. Pressure which ordinarily caused a sensation of touch or pain produced no effect upon consciousness when applied to a fold of skin raised into a ridge; thus proving that the sensations that are present are not due to any end organ remaining in the skin. Deep pressure or jarring contact, however, was quickly perceived and localized with accuracy. If we cocainize the skin, vibration will be appreciated over the area, but the appreciation will be about 80 per cent. of the normal, showing that the stimuli have been blocked to a certain extent by the anaesthetic.

The experiments of Rivers and Head have shown us that so far as the peripheral nerves are concerned the sensation of touch is distinct from that of deep pressure, and it is possible to show that vibration of a small tuning-fork over anaesthetic skin is not noted, although a fork of greater amplitude produces sensation. It seems plausible, therefore, to think that, if a vibrating tuning-fork is applied to the skin, both the sensibility to light touch and also the sensibility to deep pressure would be stimulated.

Rivers and Head show that the peripheral afferent impulses for touch and pressure, arriving by way of the superficial and deep systems, become combined in the spinal cord; so that the lightest perceptible touch produces a minimal tactile impulse, which passes up the spinal cord among the tactile impulses evoked by the severer stimulus of pressure. Cases of injury to the cervical cord showed these observers that the impulses of deep pressure and touch crossed in the cord, but much more slowly than those of pain, heat, or cold. Consequently, two paths are open to tactile impulses: one in the primary system of the posterior column, the other in the secondary intramedullary system on the other side, where they have become separated again.

We can now consider the question of the path followed by the vibratory sensation as recorded by neurologists. Bing (9) quotes a case of traumatic

haematomyelia in which there was marked affection of the sensations for pain and temperature, but no diminution of the vibratory sensation. Post mortem, the grey matter of the cord was completely destroyed at the site of the lesion. He concludes that the sensation is probably conducted in the posterior column of the white matter of the spinal cord.

R. T. Williamson quotes a case of syringomyelia in which there was marked atrophy of the hand muscles, and loss of sensations for pain and temperature on the hands and arms, but very slight impairment of tactile sensation. The sensations of pressure and vibration were quite normal. From this he concluded that the sensations of pain and temperature were dissociated in the cord from the vibratory and pressure sense.

Bing (9) also quotes a case of an extra-dural unilateral fibrosarcoma of the cervical region of the cord, causing loss of sensation for pain and temperature and diminution of tactile sensations on the side opposite the lesion, whilst on that side the vibratory sensation was normal. On the same side as the unilateral spinal lesion there was loss of the vibratory sensation, though the sensations of pain, temperature, and touch were normal. There was impairment of the sensations of position and movement in the same parts as the loss of the vibratory sensation.

We note that on the side of the lesion: (1) Tactile sensations were present; in other words, those fibres from the epicritic system entering the posterior roots had crossed over the cord. (2) Sensation of position and movement was impaired. (If the lesion had been complete these deep sensations should have been lost. Head and Thompson, *Brain*, 1906, p. 639.) (3) The vibratory sensation was absent.

The fibres carrying the sensation of deep pressure cross high in the cord, and it seems probable that the lesion was below the crossing.

These observations point to the following conclusions: (1) We are dealing with a sensation that is dissociated from those of pain or temperature. (2) It is associated with the sensation of pressure. (3) It passes up in the posterior column, and crosses high up, or not at all. These conclusions are up to now in agreement with Head's views on the paths of deep pressure.

If we now turn to the series of tabetic patients we find that the vibratory sensation is in close relation to deep sensibility. If the table on p. 57 is consulted, it will be seen that the intensity of Romberg's sign goes parallel with the diminution in the appreciation of the vibratory sensation over the lower limbs. When Romberg's sign was well marked, as in Case XV, the vibrations were not appreciated over the malleoli on either side, or the tibia on the right. On the left side the duration of appreciation was only three seconds. In Case III, Romberg's sign was very slight, and there was only about 20 per cent. diminution in the sensation. This connexion had been noted by Seiffer and Rydel (1), who stated that ataxy and lack of bone sensibility are usually found together. In Cases II, VII, IX, XI, XII, XV, there was marked diminution in the sensation of deep pressure over the lower limbs, as well as marked impairment in those

of movement and localization. Again, in my series of cases of nerve injuries, the loss of the vibratory sensation does not run parallel with the cutaneous sensory nerves injured. In Case X the musculo-spiral and ulnar were completely divided and the musculo-cutaneous and median incompletely, yet the patient's power of appreciating the vibration was about 40 per cent. of normal.

It seems, therefore, reasonable to infer that the vibratory sensation follows closely the paths of deep sensibility. Clinically there seems to be considerable difficulty in going any farther, as we have shown that the vibratory sensation may be impaired when the other deep sensations appear normal.

For the present, therefore, it seems best to content ourselves with the statement that the vibratory sensation appears to be a mixed sensation and closely allied to 'deep sensibility'.

The vibrations of a tuning-fork excite those stimuli which produce deformation of structure, but there is a possibility that they also give rise to the cutaneous sensation of pressure.

TABLE.

Case.	Int. Mal.		Ext. Mal.		Tib.		Romberg's Sign.	Sacrum.
	R.	L.	R.	L.	R.	L.		
I.	$\frac{13}{27}$	$\frac{13}{27}$	$\frac{12}{28}$	$\frac{14}{28}$	$\frac{18}{29}$	$\frac{16}{29}$	Not marked	$\frac{12}{20}$
II.	$\frac{2}{27}$	$\frac{4}{27}$	$\frac{3}{28}$	$\frac{5}{28}$	$\frac{5}{29}$	$\frac{9}{29}$	Well marked	$\frac{8}{20}$
III.	$\frac{20}{27}$	$\frac{24}{27}$	$\frac{20}{28}$	$\frac{21}{28}$	$\frac{17}{29}$	$\frac{17}{29}$	Very slight	$\frac{10}{20}$
IV.	$\frac{11}{27}$	$\frac{14}{27}$	$\frac{12}{28}$	$\frac{16}{28}$	$\frac{14}{29}$	$\frac{15}{29}$	Slight	$\frac{11}{20}$
V.	$\frac{22}{27}$	$\frac{15}{27}$	$\frac{18}{28}$	$\frac{17}{28}$	$\frac{15}{29}$	$\frac{15}{29}$	Slight	$\frac{14}{20}$
VI.	$\frac{15}{27}$	$\frac{12}{27}$	$\frac{15}{28}$	$\frac{12}{28}$	$\frac{12}{29}$	$\frac{12}{29}$	Slight	$\frac{8}{20}$
VII.	—	—	—	—	—	—	Very marked	—
VIII.	$\frac{19}{27}$	$\frac{16}{27}$	$\frac{17}{28}$	$\frac{14}{28}$	$\frac{18}{29}$	$\frac{14}{29}$	Slight	$\frac{9}{20}$
IX.	$\frac{9}{27}$	$\frac{9}{27}$	$\frac{17}{28}$	$\frac{8}{28}$	$\frac{9}{29}$	$\frac{10}{29}$	Marked	$\frac{2}{20}$
X.	$\frac{17}{27}$	$\frac{19}{27}$	$\frac{17}{28}$	$\frac{16}{28}$	$\frac{19}{29}$	$\frac{16}{29}$	Very slight	—
XI.	$\frac{9}{27}$	$\frac{9}{27}$	$\frac{8}{28}$	$\frac{8}{28}$	$\frac{12}{29}$	$\frac{9}{29}$	Marked	—
XII.	$\frac{4}{27}$	—	$\frac{12}{28}$	—	$\frac{9}{29}$	—	Marked	—
XIII.	$\frac{17}{27}$	$\frac{20}{27}$	$\frac{22}{28}$	$\frac{22}{28}$	$\frac{17}{29}$	$\frac{17}{29}$	Slight	—
XIV.	$\frac{17}{27}$	$\frac{15}{27}$	$\frac{16}{28}$	$\frac{17}{28}$	$\frac{14}{29}$	$\frac{16}{29}$	Slight	—
XV.	—	—	—	—	—	$\frac{3}{29}$	Very marked	—

— denotes that the vibratory sensation was absent.

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A STUDY OF A SERIES OF CASES OF INJURY TO THE CHEST, SEEN AT THE BASE

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The subject of chest wounds received scant attention before the War. It has come into great prominence lately, and possibly a study of these cases will be of value, since they were seen under unusually favourable circumstances. In the first place, this hospital, situated at the Base, receives patients direct from the field ambulances by train and also from the casualty clearing stations by barge. In the former instance they are admitted within two or three, and in the latter usually within six or eight, days of their wound. Secondly, they are not transferred until their general condition allows this with perfect safety. Their stay here, therefore, is sometimes several months, and although the very early and the late stages are not seen, an estimate as to the ultimate prognosis can generally be formed. The cases under consideration were admitted between February 1916 and March 1917. Their number, which was 4·7 per cent. of the total number of admissions from all causes, was 129, and made up as follows:

Bullet wounds	40
Shell wounds	80
Crushing injuries	9

Classification.

The most satisfactory classification is one based on the pathological lesion. Experience has shown that every variety of intrathoracic injury can be produced by any kind of missile, whether it actually penetrates the pleura or not, and even by traumatism without external wound.

General differences between bullet and shell wounds. Bullets usually perforated the pleura and were either not retained or lay just under the skin on the opposite side to that of the entry wound. The ribs, as a rule, either escaped injury, or, if there was a fracture, there was generally a notching or a clean perforation which gave rise to little pain. If a haemothorax resulted, it was rarely infected, and both entry and exit wounds healed without suppuration. With shell wounds, on the other hand, non-penetration of the pleura,

comminuted fracture of the ribs, retention of metal, and infection of the haemothorax were common. These facts are shown by the following figures:

	No.	Retained Metal.	Sterile Haemothorax.	Infected Haemothorax.
Bullet wounds	40	9	36	3
Shell wounds	80	58	31	29

R. D. Rudolf (1) agrees that infection of a haemothorax is infinitely more common with shell than with bullet wounds, but Rose Bradford and Elliott (2) find this to a lesser extent. Thus, in their series of haemothorax caused by shell and bullet wounds, one-half of the former and one-quarter of the latter were infected. The corresponding figures in our series were one-half and one-thirteenth respectively.

Features of the crushing injuries. This variety of injury as seen here was severe. Haemothorax, traumatic pneumonia, pneumothorax, haemopericardium, and simple pleurisy were all met with, but in no instance did an empyema result. There were usually fractures of the ribs and haemoptysis was common.

The side of the chest most often affected. In the patients who reach the Base, wounds of the right greatly outnumber those of the left side of the chest. This was at first thought to be an accident, but the explanation obviously is that a far greater number of those with left-sided wounds die in the earlier stages. Unfortunately no record was kept as to the side affected, but the proportion of right- to left-sided wounds would be about three to one.

Common Symptoms and their Significance.

Generally speaking, the patients were less ill in proportion to the pathological condition than one would have expected. This was doubtless due to their age and healthy condition before the injury. The journey, however, had exhausted the men out of proportion to its length, and their appearance showed a striking improvement after they had settled down in bed. Except in cases of emergency, therefore, several hours were allowed to elapse before they were examined. The effect of the journey was especially injurious in one case. The patient had suffered from an infected haemothorax and resection had been done some weeks previously. He had been exceedingly ill, but for a week before his arrival the temperature had been normal and the pulse-rate was below 100. On admission here he was very distressed. The temperature was 103° and the pulse 120. He remained in a dangerous state, with a high temperature and a rapid pulse, for about a week, although there was very good drainage and nothing was found to account for his condition. After this he gradually improved and the pulse and temperature again settled.

Haemoptysis. This was common, but was never dangerous, and had usually ceased before the patients arrived at this hospital. Obviously it is a sign

of injury to the lung, but many patients suffered from haemoptysis when there had been no penetration of the pleura, and in some instances all signs of intrathoracic injury had disappeared by the time when the patients were admitted. On the other hand, haemoptysis is sometimes absent even when the signs and the position of the wounds indicate that the missile has certainly penetrated the pleura. The amount and duration of the haemorrhage did not bear any relation to the severity of the lesion, but it was found that it persisted for the longest time in some of the cases of 'traumatic pneumonia'. Its usual duration in cases of haemothorax seemed to have been from two to five days. When the haemoptysis was still present on admission it was noted that its subsidence was abrupt and that the blood remained of a bright colour until it ceased.

It is very important to know how soon after the wound patients may be moved without the risk of fresh haemorrhage, in order that they may be evacuated at the earliest possible moment to the Base, where the best conditions exist for bacteriological and surgical work. Rose Bradford and Elliott's experience shows that death from haemorrhage need not be feared after the third day.

Pain. Patients suffering from dry pleurisy, pneumonia, or an infected haemothorax usually complained of pain. When, however, the haemothorax was sterile, even if there were fractured ribs, pain did not persist for more than a few days. Possibly the reflex immobility of the diaphragm and chest-wall, found in cases of intrathoracic injury, is sufficient to prevent pleural pain unless sepsis also is a factor in its causation.

Tenderness. This, together with hyperaesthesia of the skin at a distance from the wound, is a most valuable sign. In the case of a haemothorax it may be the first indication of the onset of infection. It must be remembered, however, that surgical emphysema is often tender (4).

Dyspnoea and cyanosis. These were common in patients suffering from pneumonia and septic haemothorax. In the latter they were early and valuable indications of sepsis, and out of all proportion to the quantity of fluid present. Rose Bradford (2) considers these signs and sleeplessness as most reliable evidence of infection. Patients with a sterile haemothorax, on the other hand, were not dyspnoeic or cyanosed unless the collection of fluid was very large and caused considerable displacement of the heart, and even under those circumstances usually only on exertion.

Sleeplessness. Sleep was little affected unless there was pneumonia or an infected haemothorax. In the latter class of case, sleeplessness was a very troublesome symptom, which usually persisted until the patient could be allowed out of bed for part of the day.

Loss of weight. The extreme and rapid wasting is a striking feature shown by patients suffering from a septic haemothorax. It was found to be an infallible sign of infection which in no other situation brings about such a rapid loss of flesh.

In the case of a sterile haemothorax the appetite remains good and there is no wasting.

Jaundice. This was never deep. It was seen in some of the cases of sterile haemothorax, but more often when the latter was infected or there was traumatic pneumonia. Its occurrence did not *per se* seem to indicate a bad prognosis. Elliott and Henry (13) attach great importance to definite jaundice occurring in cases of haemothorax as an indication of infection, generally by anaerobic organisms.

Hiccough and vomiting. These symptoms were not common. Nearly always when they occurred there was an abdominal lesion.

In Rose Bradford and Elliott's (2) experience vomiting invariably indicated an abdominal injury.

Surgical emphysema was never extensive. Its only importance was that a pleural rub, râles, or a pneumothorax might be simulated, or the impaired note on percussion due to fluid masked. The other signs, however, should prevent false conclusions being drawn.

The following varieties of lesions were seen:

1. Penetrating or non-penetrating wounds with no signs of intrathoracic injury.
2. Pleurisy, with and without effusion.
3. Pneumonia.
4. Pericarditis and intrapericardial lesions.
5. Sterile haemothorax.
6. Infected haemothorax.
7. Abdomino-thoracic injury.

Massive collapse, bronchitis, oedema of the lung, fractured ribs, and surgical emphysema also occurred as complications of the above-mentioned conditions.

Stephenson's series of 214 cases in the South African War included:

Sterile haemothorax	62
Infected haemothorax	32
Abdomino-thoracic injuries:	
Probable	8
Certain	2
Mortality	14 per cent.

Other complications met with by us and often due to a separate wound were: thrombosis of the axillary vein, 2; subclavian aneurysm, 1; thrombosed femoral vein, 1; fracture of the clavicle, 1; fracture of the humerus, 1; fractured olecranon, 1; fractured femur, 2; spinal concussion, 4; injury, organic or functional, to the brachial plexus or nerves, 4; other nerve injuries, 2.

Penetrating or non-penetrating wounds with no signs of intrathoracic injury.

Many instances of this kind of wound were seen. In some, haemoptysis occurred even when it was unlikely that the pleura had been penetrated. In others there were no abnormal signs or symptoms, although it was certain, from the positions of the entry and exit wounds, that penetration must have taken place. Most of these were examined with the X-rays as a safeguard in spite of the absence of abnormal signs. Unfortunately for statistical purposes, no record was kept either as to their number or as to the kind of projectile which had produced the wound.

Rose Bradford and Elliott (2) also found that the chest-wall and pleura might undergo laceration without a haemothorax resulting.

Pleurisy. There were ten cases of dry pleurisy unassociated with other intrathoracic lesions. The condition was as a rule accompanied by fractured ribs, and was often caused by a missile which had grazed the chest-wall but had not penetrated the pleura. Traumatic pleural effusion was found in two instances, but in neither of these did the fluid become infected. The course of the disease was mild, constitutional disturbance being slight and the temperature, which rarely rose above 101°, subsiding in five or six days. For treatment Dover's powder was especially useful, and the affected side of the chest was usually immobilized by strapping. The occurrence of pleural friction sounds after aspiration was common. The signs persisted for a few days, but no constitutional disturbance and little or no pain were caused. It is said by Hull (9) that one frequently meets with cases of fractured ribs and a resulting pleurisy on the side of the chest opposite to that of the main lesion, and that the condition is due to the fall of the patient after he is hit. This, however, was not seen in our series, although it was not unusual to find hypostatic pneumonia at the opposite base. As a rule the occurrence of pleurisy on the opposite side of a haemothorax is an indication that the latter is infected.

Pneumonia. Two distinct varieties were seen: (*a*) typical pneumococcal lobal pneumonia, as a complication of haemothorax, and (*b*) so-called traumatic pneumonia. Of these the latter variety was the more common and presented features quite different from those of the former. Hypostatic pneumonia often complicated other lesions and was frequently a terminal condition. It is not, however, included in either of the following descriptions.

Pneumococcal lobar pneumonia. This occurred in six patients. In every instance there was the usual 'rusty' sputum, although this revealed itself only after the cessation of the brighter red haemoptysis due to the lung wound. The temperature was in every case high, and the signs and general features were quite typical. In three of the patients the septicaemic nature of the disease was demonstrated. In one the haemothorax on the opposite side was infected by pneumococci, which were also found in pure culture in an abscess which developed in the buttock round a shell fragment. In another, also, the haemothorax was infected by pneumococci.

In a third patient there was a large abscess, due to the shell wound, between the ribs and the pleura. Pneumonia developed in the lower lobe of the lung of the affected side and was followed by an empyema and a virulent enteritis, both of which were proved bacteriologically to be pneumococcal. This same patient also suffered from a very extensive erysipelas, but after many weeks of acute illness made a good recovery.

It is rare for pneumonia and a haemothorax to coexist on the same side. The explanation usually given (4) is that the lung is rendered immune to infection owing to its compression by the fluid. This explanation, however, does not seem rational. Although rest is essential for an inflamed organ, one would have supposed *a priori* that the stasis and retention of secretion in the compressed and immobile lung would have been a factor strongly predisposing it to infection. The beneficial effect of an artificial pneumothorax in phthisis is not a parallel example. In this case the lung is benefited indirectly and not as a direct result of its compression, since the pneumothorax, by compressing and rendering immobile the source of infection, reduces its blood-supply; the dissemination of toxins is thus lessened, and in this way the resistance of the patient is raised and the infection in the lung overcome.

In one instance only was the lung on the side of the haemothorax affected. This patient had suffered from a haemothorax which had been aspirated twice, the fluid on each occasion being reported sterile. Convalescence was advanced and the patient was walking about, when he suddenly, about a month after the wound, developed pneumonia on the side of the haemothorax. A streptococcal empyema resulted which necessitated rib resection and drainage.

Although it might have been expected that pneumonia affecting the sound lung would have been a very grave complication of a haemothorax, only one of the patients in whom this was the case died. Probably the condition is not more serious than a bilateral pneumonia, which is said by many not to bear a worse prognosis than one affecting a single lobe of the lung.

Traumatic pneumonia. A form of atypical pneumonia was seen somewhat frequently and has been termed 'traumatic'. Pathologically the condition is probably due to areas of bruising and infarction of the lung. The diagnosis was made in sixteen cases, of which nine were the result of shell wounds, six of bullet wounds, and one of a crushing injury. The pleura was penetrated in fourteen instances. The features of such cases were distinct. There were usually, but not invariably, fractured ribs, but in every instance there were extensive signs of dry pleurisy.

Only one of these patients was dangerously ill, and the symptoms consisted of pleural pain, sleeplessness, slight dyspnoea, and loss of appetite. There was usually a moderate degree of cyanosis. The temperature, highest in the evening, rarely rose above 102°, and generally persisted for from two to five weeks and came down to lysis.

The pulse-rate was rarely above 100. The sputum was copious and often offensive; it was never 'rusty', but was often tinged with bright blood, and this

sometimes persisted for as long as three weeks. In only one case was there an effusion of fluid. This was at first clear, later turbid, and was found to contain streptococci. Resection was performed and the man made a good recovery.

Diagnosis. The signs were somewhat atypical of pneumonia. There was always an impaired note, often as pronounced as that produced by fluid. This sign was useful in the differential diagnosis from simple pleurisy. A pleural rub was invariably present. No alteration of the position of the heart was ever found. This fact and the presence of fine râles, which were always heard, and the pleural rub were the most valuable signs in the differential diagnosis from a haemothorax. Often coarse rhonchi indicated the existence of coincident bronchitis. Definite bronchial breathing and bronchophony occurred in the minority of cases, diminished breath and voice sounds being more usual. The disease always affected the lung on the side of the wound. The X-rays were nearly always employed in order to confirm the diagnosis, the comparative transparency of the affected side and the absence of displacement of the heart differentiating the condition from a haemothorax. In some cases, however, it was necessary to make use of the exploring needle. Unfortunately no bacteriological investigations of the sputum were carried out.

Treatment. An expectorant mixture containing ammonium carbonate gr. iv and potassium iodide gr. v to the ounce was found to be beneficial, and, when the sputum was offensive, inhalation of tinct. benzoini co. (one drachm to the pint of hot water) seemed to lessen the foetor. The patients were allowed in a chair for a short time by about the tenth day, even if by then the temperature had not quite settled to normal. Open-air treatment was employed during the daytime whenever possible. It is probable that vaccine treatment would be of some value in hastening resolution in these cases.

Condition on transfer to England. Although some of the patients were kept under observation for several weeks, in no case had the abnormal signs completely disappeared. There always remained a slightly impaired note on percussion, diminished breath sounds, and fine râles. The general condition nevertheless was good, the temperature being normal and the pulse below 100, and the patients being able to walk about without discomfort.

Abscess and Gangrene of the Lung.

These conditions were not seen. This is somewhat surprising in view of the frequency of retained metal and clothing. All of the patients, however, who had suffered from 'traumatic pneumonia' were transferred to England, and therefore lost sight of, before the lung signs had completely disappeared, and it is possible that in some of them signs of cavitation would reveal themselves when no longer masked by the signs of resolving pneumonia and bronchitis. This, however, is improbable, since Hale White (5), in speaking of cases in England, also lays stress on the rarity of the above-mentioned conditions.

Massive Collapse of the Lung (6).

Many observers have found that this condition of the lung on the opposite side to that of the main lesion is a very common complication. This was not, however, the experience here, but it is possible that a false impression was obtained, since the majority of the patients were not seen until about a week after their wound, so that the condition, even if it had been present, might have passed off. The signs in the lung resemble those of pneumonia, but the characteristic feature is that the heart is drawn over to the affected side. If, however, there is a haemothorax, the diagnosis is difficult, since it is uncertain whether the displacement of the heart is due to the haemothorax or to the collapse.

Although in several instances the presence of collapse affecting the opposite lung was suspected, the diagnosis was made with certainty in two cases only. In neither of these was there a haemothorax.

1. This patient was admitted four days after his wound. The right side of the chest had been perforated by a bullet. The heart was displaced about two and a half inches to the left and the signs at the left base were an impaired note, faint bronchial breathing, and fine râles. There were no abnormal signs on the right side. X-ray examination showed that there was no haemothorax and that the heart was displaced to the left. The patient was very little distressed and the abnormal signs disappeared in the course of a few days.

2. This patient furnished a very striking example of the condition. There were fractured ribs on the right side due to a shell wound, but no haemothorax had resulted, and there was no evidence that the pleura had been penetrated. The patient had been comfortable until the third day after his wound, when he suddenly became distressed and the temperature, which had been normal, rose to 103·6°. This had happened during the journey a few hours before admission to this hospital. On admission he was very dyspnoeic and cyanosed. The pulse was rapid and weak. The apex beat was displaced to the left mid-axillary line. On the left side there was no air entry into the upper lobe and a very impaired entry into the lower lobe. There was no fluid in the right pleural cavity. Oxygen gave some relief, and three doses of a mixture containing ammonium carbonate gr. x were given at two-hourly intervals. During the night the patient expectorated a large quantity of tenacious sputum, and by the morning was free from distress, by which time it was found that the displacement of the heart had righted itself and that the only abnormal pulmonary signs were those of bronchitis, which persisted for a few days. The probable explanation of the collapse of the lung is that the bronchi become plugged with secretion. If the condition is due to paralysis of the diaphragm, as some authorities suppose, it is difficult to explain the displacement of the heart to the affected side.

Pericarditis and Intrapericardial Lesions.

These complications were less common than might have been expected. A pleuro-pericardial rub was frequently heard in cases of left-sided haemothorax, but was transitory and of little clinical significance. Rose Bradford and Elliott point out that a pericardial rub is often evidence of a small sterile haemopericardium.

Pericarditis without effusion. This was found in four patients. In two the condition was associated with haemothorax infected by anaerobic organisms. One of these patients made a perfect recovery after a single aspiration, but the other needed resection. In another patient a rub was heard for the first time after aspiration of a sterile haemothorax. It persisted for two days, but there was no constitutional disturbance or pain. In another instance a rub was present for a few days in a case of sterile haemothorax, but was without clinical significance. Possibly in some of these cases the rub was not a true intrapericardial one, although clinically it was indistinguishable from such. Elliott and Henry (13) state that many apparently pericardial rubs are really due to the presence of gas in the mediastinal tissues.

Pericarditis with effusion. There were three examples of this. In two the effusion was purulent and occurred in fatal cases of infected haemothorax, for both of which resection had been performed. In one of these a rub was heard, but in the other, although some cardiac lesion was suspected from the general features of the case, the only signs indicating that there might be a collection of fluid in the pericardium were those of compression of the lower lobe of the left lung—bronchial breathing, bronchophony, râles, and an impaired note. No enlargement of the area of cardiac dullness could be made out, and this fact was probably due to compensatory emphysema of the upper uncompressed lobe and to the presence of the resonant empyema cavity on the right side. The diagnosis could, of course, have been made by means of the X-rays, but unfortunately the patient was too ill for this to be done. At the autopsy a large collection of pus was found in the pericardium.

In the third case, the patient was admitted with a small right-sided haemothorax. He was exceedingly ill, and there was an extensive pericardial rub and definite signs of a pericardial effusion. This was verified by means of the X-rays. The haemothorax was aspirated, 15 ounces being drawn off. This fluid was found to contain streptococci, but, on account of the rapid improvement of the patient, resection was not performed. One other aspiration was found necessary. The abnormal cardiac signs disappeared completely. (Case V in Appendix.)

Haemopericardium. Three instances of this condition were seen. One patient had been severely crushed. There was extensive bruising on the left side and a small wound on the right side of the chest. On admission there was a small sterile serous effusion on the right side and pneumonia on the left.

There was much purulent bronchitis. The cardiac dullness was increased in all directions. The patient was very distressed and had a high temperature. A needle was put into the pericardium and about 5 ounces of blood, under considerable tension, were aspirated. An empyema developed on the right side, but the patient ultimately made a good recovery.

In another patient there was a perforation of the first part of the aorta. He was known to have had a small haemothorax, but had been quite undistressed until the sixth day after the wound. He had then suddenly collapsed and become pulseless. Death occurred twelve hours later. At the post-mortem examination it was seen that there was a minute perforation of the pericardium and of the first part of the aorta. The pericardial sac was distended with blood and there was a small right-sided haemothorax.

Presumably the aorta was not completely perforated at the time of the injury, the sudden collapse on the sixth day being due to the lumen being opened by ulceration. In this case, too, the only signs of fluid in the pericardium were those of compression of the left base. It is important, therefore, to recognize this fact and to suspect a pericardial effusion when the cardiac distress is out of all proportion to the pulmonary lesion and to the degree of sepsis. (Case III in Appendix.)

A case of great interest and rarity was one in which simple fracture of the ribs, caused by a crushing injury, gave rise to a pneumo-haemopericardium. Here there was very little distress and the diagnosis was made on the presence of 'churning' sounds and verified by means of the X-rays. Ten ounces of blood and a considerable quantity of air were aspirated from the pericardium and the patient made a good and rapid recovery. (Case I in Appendix.)

The general conclusion to be drawn is, that mere damage to the pericardium, unless complicated by sepsis or by gross lesion of the heart, is without serious significance and not to be compared with disease of the pericardium occurring in the course of acute rheumatism or a septicaemia, the bad prognosis in those conditions being due to the severity of the damage to the heart muscle, of which the pericarditis is merely the index.

Pneumothorax

uncomplicated by haemothorax, sterile or infected, was not met with. This is opposed to the experience of R. D. Rudolf (1), who states that pure pneumothorax is not uncommon, but that haemopneumothorax is rare. In our series there were seven instances, four of which were associated with sterile and three with infected haemothorax. In Rose Bradford and Elliott's (2) 320 cases of haemothorax there were eight, and in Hale White's (5) series of 50 there were only two, cases of pronounced pneumothorax. Possibly the condition would be more frequently found if an examination for its detection were made quite soon after the wound. In the only patient in this series who was seen on the same day as his wound, a pneumothorax was present on admission, but the air was absorbed

in a few days. Rudolf (1), however, finds that a pneumothorax may develop after some days, although it was not present at first. In one instance only was the pneumothorax proved to be the result of a gas-forming organism, in this case Bac. aerogenes encapsulatus.

Elliott and Henry (13) warn against the danger of mistaking a pneumothorax associated with a sterile haemothorax for pneumothorax due to gas-producing organisms. In two patients a pneumothorax was found only after aspiration of a sterile haemothorax. The explanation of this was difficult, since on each occasion the cannula was removed from the pleural cavity while still connected with the vacuum bottle, and, since there was no fresh haemorrhage, it was very improbable that there had been any injury to the lung.

Diagnosis. A pneumothorax was sometimes simulated by skodiac resonance above the level of the fluid in a haemothorax. This, in conjunction with the reflex immobility of the diaphragm, gives rise to hyper-resonance and greatly diminished breath sounds. The most valuable signs are the 'coin' sound and the reverberation heard when the patient coughs. The diagnosis was never made if these signs were absent, although Rudolf states that the 'coin' sound is often absent.

Treatment. Since pure pneumothorax did not occur in this series, the necessity for treating it did not arise. In dealing with a haemopneumothorax it was found advisable to draw off the fluid before the air. If the end of the cannula inside the thorax is raised so that the air is removed before the fluid, some indication may arise for terminating the aspiration while there is still fluid left in the chest. If, however, all the fluid is withdrawn first, any remaining air will be absorbed spontaneously.

Haemothorax.

This was the commonest result of a chest wound. The number seen was 91. Of these 60 resulted from shell, 29 from bullet wounds, and 2 from crushing injuries without external wound; 32 were infected and 59 were sterile. It will be noticed that about two-thirds remained uninfected. In Rudolf's series, and also in Rose Bradford and Elliott's, this figure was three-fourths. Double haemothorax was not seen.

Haemothorax may be produced by any variety of injury, often without penetration of the pleura or fracture of the ribs. Most authorities are agreed that the source of the bleeding is more often the lung than the parietes. The comparative rarity of infection after a bullet wound has already been referred to. After the diagnosis of haemothorax has been made it is necessary to watch very carefully for the first signs to lead one to suspect the onset of sepsis.

Diagnosis of haemothorax. The diagnosis of fluid was, as a rule, easy. The signs, however, may be somewhat misleading. Tactile vocal fremitus was sometimes diminished or absent, but was occasionally increased. The com-

pensatory emphysema of the sound lung and the muscular development of the patient often made it impossible to detect any displacement of the apex beat or to map out the area of cardiac dullness. Almost invariably there was 'board-like' dullness to percussion, and this was by far the most valuable sign. The presence of air in the pleural cavity, however, or of surgical emphysema, modified the note considerably. On auscultation in about half the cases there was bronchial breathing, often loud and associated with bronchophony; in the other half there were diminished breath and voice sounds. This difference in the signs is probably determined by the amount of compression of the lung, since the former signs were more usual with large than with small effusions. The absence of râles was a very strong indication of fluid, as opposed to pneumonia. Care must of course be taken not to mistake the crepitations due to surgical emphysema for true râles.

Use of X-rays. This method of examination is essential not only for the purpose of diagnosis, but also for judging the effect of treatment. The quantity of fluid was estimated by the height and degree of the opacity and by the amount of displacement of the heart. In a few instances, nevertheless, it was not possible to distinguish between fluid and solid lung without the use of the exploring syringe.

The Effect of Thoracic Injuries on the Diaphragm.

It was almost invariably noticed that the diaphragm on the affected side had a very poor range of movement, even when there were no signs of penetration of the pleura or of intrathoracic injury except slightly diminished breath sounds and the fact that a foreign body could be seen by means of the X-rays. Rose Bradford and Elliott (2), on the other hand, state that this condition of the diaphragm is seen only in cases of haemothorax. This poor movement was a late sign to disappear, being sometimes still present several weeks after the wound, and was then often the only abnormality to be seen with the X-rays, there being no opacity and the line of the diaphragm being well defined.

Sometimes the diaphragm on the affected side was quite fixed and its position was in many cases abnormally high in spite of a considerable quantity of fluid in the pleural cavity. This must be remembered when aspiration or resection is done, in order to avoid operating too low. The height of the diaphragm did not *per se* influence the amount of displacement of the heart. These phenomena are not easily explained. Probably they are reflex mechanisms intended to prevent further damage being done by movement. In this they are assisted by the rigidity of the abdominal muscles, generally noticed on the affected side. The abnormally high position of the diaphragm would suggest that it is in a condition of relaxation, i. e. paralysed. Nevertheless, when movement was seen, this, however much it might be diminished in range, always synchronized with that of the opposite side. This indicated that, although there was paresis,

there was no paralysis. Possibly the condition is sometimes due to phrenic nerve shock and is comparable to brachial plexus, sciatic, or spinal concussion.

To digress for a moment; if the condition spoken of as massive collapse of the lung and described by Pasteur (6) is caused by a paralysis of the diaphragm, it seems difficult to explain why the heart should be drawn to the affected side. One would have thought that the amount of collapse of the lung would have been proportional to the degree of rise of the diaphragm, and that the heart would have either remained unaltered in position or that it would have been displaced to the opposite side. If on the other hand the collapse of the lung is due to the bronchi being blocked by secretion, it is easy to understand that the diaphragm would be drawn up and the heart displaced to the affected side.

Clinical Appearance, Treatment, and Course of an Uninfected Haemothorax.

After a few days the patients were comparatively comfortable and did not suffer from dyspnoea, and were not cyanosed unless the collection of fluid was large enough to displace the heart considerably, and even then usually only on exertion. Sleep was easily obtained, by means of mild opiates if necessary, and appetite was little affected. The wasted appearance so typical of infected cases was never acquired. Pain was rarely complained of and there was generally no tenderness of the affected side. Constipation was sometimes obstinate. The improvement from day to day was rapid and steadily maintained. In no instance did the patient show the pallor which is always seen with other severe internal haemorrhages. This fact was also mentioned by R. Murray Leslie (14), and is very remarkable, but is possibly to be explained by the fact that the haemothorax compresses the lung so that the same quantity of blood is in the general circulation as before the injury. Hale White explains the absence of pallor by supposing that the fluid in a haemothorax consists not only of blood but also largely of a serous effusion due to the irritation of the pleura. It would be of interest to find whether blood-counts both of the haemothorax fluid and of the circulating blood and blood-pressure determinations would throw any light on the explanation.[1]

The temperature varied between 100° and 103°, and in most cases did not persist for more than about fourteen days, its usual duration being from six to ten days. When, however, there was a moderate-sized collection, even though sterile, which had not been aspirated, the temperature persisted for as long as four or five weeks after the wound. Haemoptysis has been spoken of earlier, and had usually ceased by the time when the patients were admitted here. Cough was rarely troublesome and easily controlled by a mixture containing codein or by injections of morphia. In fact, it is very important that, until aspiration can be performed, free use of morphia should be made, if the patient shows any tendency to cough or to become restless.

[1] Examinations carried out since the completion of this paper have shown that there is always a diminution in the number of red cells, there often being less than 1,000,000 per c.mm.

Treatment. At the beginning of the War aspiration of sterile haemothorax was opposed by many on various grounds. This view, however, is now no longer generally held, and nearly all authorities are agreed that a haemothorax, if of moderate size, should be aspirated and not be allowed to undergo spontaneous absorption. The immediate prognosis is quite good without mechanical removal of the fluid unless the collection is large enough to cause dangerous embarrassment to the circulation, but the ultimate effect of leaving all except very small effusions without interference must be serious. Experience has shown that the objections of those opposed to aspiration rest on theoretical considerations which practice does not confirm.

In this series there were only four instances of clotting enough to interfere with efficient aspiration, and on no occasion was there a recurrence of the bleeding after aspiration. As regards exploratory needling, this never causes sepsis if aseptic precautions are taken, and is very often called for owing to the frequently misleading nature of the signs and the necessity of making an accurate diagnosis as early as possible both as to the presence or not of fluid and, more important, as to its sterility.

In view of the nature of the fluid which renders natural absorption slow, the ever-present possibility of latent infection, and the rapidity with which a rigid layer of organized fibrous tissue may encapsule the lung (this has been seen at autopsies on septic cases as early as three weeks after the wound), it is essential to aspirate a haemothorax on at least the same indications as one would a clear effusion. Rose Bradford goes so far as to say that he sees no definite objection to aspiration of all cases, but insists that, at any rate, this should be done when the dullness reaches as high as half-way up the scapula. The practice here was to aspirate when either the dullness reached the inferior angle of the scapula, or when the X-ray appearance indicated that there was more fluid than the signs suggested, the dullness having been masked either by surgical emphysema or a pneumothorax.

Time chosen for aspiration. Judging by the condition of the patients when they were transferred, it would seem that the best results are obtained if aspiration is not delayed for more than about a week after the wound. Several cases were aspirated earlier than this, i. e. on the fifth day, but the ultimate results were not better than those obtained by waiting until the seventh or eighth day, so that on account of the increased risk of a recurrence of the haemorrhage after such early removal of the fluid, the day chosen was the seventh or eighth, it not being necessary to take into account the size of the haemothorax.

Number of aspirations necessary to empty the chest satisfactorily. Of the 33 cases of sterile haemothorax which were aspirated, 17 needed only one aspiration, 6 required two, 7 three, and in 3 instances aspiration, though repeated several times, was ineffectual, and it was necessary to evacuate the clot by open operation. As a rule, if the effusion exceeded 25 oz., more than one aspiration was found to be necessary.

Technique of aspiration. Local anaesthesia was always employed, a preliminary injection of morphia (gr. $\frac{1}{6}$–gr. $\frac{1}{2}$) being given half an hour beforehand. The local anaesthetic employed was 1 per cent. novocaine, to each drachm of which adrenalin (α) v of the 1 in 1,000 solution) was added. The site chosen for the puncture was the fourth or fifth space in the mid-axillary line. The patient could then lie in a comfortable position during the operation, and it is said (4) that, if there is any clotting, the fluid is best reached by a puncture made well forward. In practice it was found that the fluid was seldom missed when the needle was inserted in this position. A small incision with a scalpel facilitates the introduction of the cannula and also allows it to be moved in and out with little force. The advantage of this is that an estimate can be formed as to the size of the cavity, since resistance is easily felt when the distal end of the cannula touches the walls. If the flow was scanty, the cannula was connected with the vacuum bottle exhausted to the necessary degree. If, however, the flow was free, the fluid was allowed to run out under the influence of gravity, since in this way more could be withdrawn with less distress to the patient. When aspiration is finished, it is important not to disconnect the cannula from the vacuum bottle before the former is withdrawn, in order to avoid the possibility of producing an artificial pneumothorax, which will tend to delay the expansion of the lung, this, on the other hand, being aided by a negative pressure in the pleural cavity.

Any of the following were taken as indications for terminating the aspiration: (1) Cough and shortness of breath; (2) cessation of the flow; (3) faintness; (4) change of colour of the fluid to a brighter red; (5) an amount of three pints being obtained.

1. *Cough and shortness of breath.* These symptoms and pleural pain came on somewhat suddenly when a certain portion of a large effusion had been drawn off, even if the chest had been by no means completely emptied. In the case of a small effusion they appeared when aspiration was almost complete. Their onset is delayed if a preliminary injection of morphia is given, and also if the fluid can be slowly run off under the influence of gravity. It is claimed that the symptoms can always be abolished if the fluid is replaced by oxygen. The probable explanation is that they are due to irritation caused by the two mildly inflamed pleural surfaces coming into contact with each other. It is unlikely that the abrupt return of the heart is a factor in their causation, since with a small effusion the displacement is very slight. If aspiration is stopped immediately the symptoms are complained of, they pass off quite soon, and have usually disappeared by the time that the patient is back in bed.

2. *Cessation of the flow.* When this happens it must of course be ascertained that there is no blocking of the cannula or tubes and that there is an efficient vacuum in the bottle. The distal end of the cannula, too, must be made to explore all parts of the cavity, especially the posterior and lower part. If, under these conditions, the flow ceases, it means that either all the fluid has been removed or that clotting has occurred in the pleural cavity.

3. *Faintness.* This was uncommon and occurred usually only in nervous patients. It can be largely prevented by a preliminary dose of morphia and by holding the patient in conversation during the operation.

4. *Change of colour of the fluid to a brighter red.* This may mean that the pleura is being damaged by the cannula and that fresh bleeding is taking place, but if the aspiration is done in the first week the fluid will be almost indistinguishable from fresh blood, and if aspiration is delayed for a fortnight or three weeks the first portion of the fluid will be sometimes comparatively clear and the last portion darker and of a thicker consistency. The appearance of this latter need not, of course, be taken as an indication for stopping the aspiration. In practice there is probably no danger of wounding the pleura, provided that the cannula used is a blunt one.

5. *An amount of three pints being obtained.* Theoretically, it would possibly be dangerous to remove more than this quantity at a single aspiration. In practice, however, other indications for terminating the aspiration generally arise before this figure is reached.

Oxygen replacement (11). It is claimed that by means of this method of treatment (*a*) effusions can be removed by the minimum number of aspirations; (*b*) the dangers and discomfort associated with the rapid removal of large effusions are eliminated; (*c*) the temperature settles rapidly and there is no constitutional disturbance after aspiration; and (*d*) a large haemothorax can be aspirated very soon after the wound without danger of fresh haemorrhage, and that this may be of great value if the effusion is large enough to cause serious embarrassment to the circulation.

Unfortunately the method was not made use of except in the case of the last few patients admitted, and it was regretted that it had not been used as a routine for all patients. The most striking advantage observed was that it was possible to aspirate a haemothorax completely at a single operation and that this could be done without the slightest discomfort to the patient. When aspiration without replacement had been performed there was always some, and in many instances very considerable, discomfort and distress to the patient. By the use of the replacement method, therefore, a single aspiration gave as good a result as multiple aspirations without replacement, and the patients were spared much unnecessary distress. Probably the ultimate results are the same, however, whether replacement is or is not practised, since in both cases it was found that if a haemothorax was sterile the temperature promptly settled and there was no constitutional disturbance after aspiration. In no instance did indications necessitating aspirations during the first few days after the wound arise, so that the effect of the replacement method in that class of case was not seen. The apparatus suggested by Hull was used and his technique was followed (8).[2]

[2] Since this paper was written a rise in temperature after oxygen replacement has occurred in several patients. This was associated with pleural pain and dyspnoea, and at first led to the false supposition that infection had been introduced. This, however, was not the case, and

Variations in the character of the fluid. The appearance of the fluid varied with the time elapsing before aspiration was performed, and there were certain differences in appearance between an uninfected and an infected fluid. The appearance of a sterile fluid, if drawn off in the first week, was almost indistinguishable from that of fresh blood. In older cases it became browner, and after a further period was clearer, and with varying degrees of blood-staining, until ultimately it was straw-coloured and resembled a serous pleural effusion. This, however, is not always the case, since in one instance, when aspiration had been delayed for over a month, the fluid only appeared different from fresh blood in that it was slightly browner. It is said (4) that a carmine-coloured froth denotes haemolysis and sepsis. This colour, however, was often shown by many sterile fluids, and therefore could not be considered as infallible evidence of infection. A foul smell was, of course, proof positive of sepsis, a sterile fluid being odourless.

Microscopical appearance of sterile haemothorax fluid. It is advisable to prepare the film immediately. If this cannot be done, sodium citrate should be added to the blood in order to prevent secondary clotting, which will spoil the appearance of the film. If the haemothorax is not of more than about a week's duration, the film presents the appearance of a normal blood film, although the leucocytes are often in excess. If the haemothorax is older, both the red and the white cells stain badly, and there is a great increase of the latter. There is also more pink staining of the ground substance with Leishman's stain than is the case with a recent haemothorax.

Bacteriology. In all cases needing aspiration, and in others if there was any suspicion of infection, films were examined and reports as to the results of aerobic and anaerobic culture were obtained. Information as to whether immediate resection was necessary could nearly always be gained from the examination of the film. More will be said on this subject when infected haemothorax is considered.

Clotting of the fluid in a sterile haemothorax. It is agreed by all and is an established fact that clotting of the fluid of a haemothorax in the pleural cavity sufficient to interfere with efficient aspiration is rare. It is difficult to find any explanation of this. Elliott and Henry (13) suggest that the absence of clotting is due to the whipping of the blood by the constant movement of the chest. The supposition that it always clotted was one of the main arguments of those opposed to aspiration, and led to many cases being left without interference in the earlier stages of the War. Doubtless slight clotting often occurs, and its amount is probably proportional to the time elapsing between the wound and the aspiration. In this series there were only four instances of clot preventing almost perfect emptying of the chest.

the symptoms passed off after several days, leaving no ill effects. It has also been found preferable to run in the oxygen only when the patients complained of discomfort. Pressure readings are not necessary, enough oxygen being given to allay the symptoms. More fluid is then withdrawn until the symptoms again show signs of recurrence.

Case I. This patient was admitted about a month after his wound. The haemothorax had been aspirated twice, 15 and 10 oz. being obtained. On admission, he had a normal temperature, a pulse of 80, and was able to walk about the ward without dyspnoea. The signs and X-ray appearance suggested that there were still about one and a half or two pints of fluid present, and there was definite displacement of the heart. Aspiration, however, failed to draw off more than 3 oz. The patient was transferred *in statu quo*, and unfortunately no information had been received as to his further progress.

Case II. This patient suffered from a large left-sided haemothorax, which displaced the heart so much that pulsations were felt beyond the right nipple. At times he became very dyspnoeic and complained of severe pain which came on in spasms. The pulse was rapid, averaging 110–120, but rising sometimes to 140. Aspiration was first performed on the seventh day, but the flow ceased when 20 oz. had been drawn off. It was repeated on subsequent days, but failed to remove more than a few ounces each time. The position of the heart, the symptoms, and the pulse-rate remained unaltered, and the temperature in the third week was still raised (about 101° in the evenings). The fluid was examined three times, but on each occasion was reported sterile. Towards the middle of the third week, since the man was becoming progressively thinner and more exhausted, it was decided to perform resection in order to evacuate the clot. At the operation it was found that there was a large cavity filled with adherent clot; this latter was washed out as well as possible by gentle irrigation, but no effort was made to dislodge it digitally or by means of instruments; a large drainage-tube was then inserted. After the operation the dyspnoea and pain were satisfactorily relieved and the displacement of the heart definitely lessened. For a few days the patient progressed well, and the pulse-rate dropped to below 100 for the first time since admission; the temperature, too, came down to a lower level.

On the onset, however, of secondary infection, the condition began to deteriorate. The temperature and the pulse-rate rose, and the patient again suffered from pain and breathlessness. His condition was very unsatisfactory for about ten days, and then again began to improve. After a few more days he was allowed in a chair for a few hours, and by the time when he was transferred to England (about a month after the operation) the temperature had finally settled and he was able to walk about in the ward. There was still a large cavity which required drainage, and the expansion of the affected lung was very deficient.

Case III. This man had a large right-sided haemothorax which displaced the heart to the left, the apex beat being felt in the mid-axillary line. Only very inefficient amounts could be drawn off by aspiration, and it was therefore decided to remove the clot by open operation. The fluid had been examined bacteriologically several times and had been reported sterile on each occasion. In view of the unsatisfactory result obtained in the last case by resection and drainage, it was thought advisable to make an attempt to evacuate the clot and then to close the chest completely. The operation was performed by Capt. F. D. Saner during the third week after the wound, and proved very successful. Primary union occurred, and, except that it was necessary, three days later, to aspirate some 15 oz. of blood-stained serum, recovery was rapid and uneventful. It was possible to allow the patient out of bed on the sixth day, and when he was transferred to England, fifteen days after the operation, he could walk about the ward without becoming exhausted. An interesting feature was demonstrated in this case, i.e. that the mediastinum becomes adherent quite early to the side to which it is displaced. Although the cavity was found to be definitely smaller at the end of the operation than at the beginning, the position of the apex beat was little altered, and although immediately after the aspiration, performed three

days later, the apex beat was nearly in its normal position, this was probably merely due to the negative pressure produced on the right side, since it again receded and only gradually returned, until, at the time of transfer, it was half an inch outside the nipple line. (Case IV in Appendix.)

Case IV. This patient suffered from a large right-sided haemothorax. The apex beat was displaced to the left axilla and the man became progressively more distressed. Repeated attempts to aspirate were made, but each time only a few ounces could be withdrawn. Each specimen, however, was reported sterile.

In the third week from the wound the pulse was very poor and the left lung showed signs of compression. Since it appeared probable that recovery would not take place without operative interference, it was decided to remove the clot. Thoracotomy was performed, and about two pints of clot were removed. The wound was closed completely. For three days the improvement was very satisfactory. Fluid then accumulated in the right pleural cavity. This was aspirated and found to contain streptococci. Resection was performed, but this made little difference to the general condition, and the patient died three days later. The cause of death was sepsis occurring in a patient already exhausted by circulatory embarrassment.

Treatment when clotting of the fluid occurs and interferes with efficient aspiration. This subject seems to be somewhat neglected, and one about which little has been written. This is unfortunate, since, although an uncommon one, the condition, if present, is difficult to treat. In a Memorandum issued by the War Office (4), it is said that, if aspiration fails on account of clotting, other attempts will be useless until several weeks have elapsed. The experience here, however, suggests that the hope of a clot ultimately becoming fluid is unfounded on fact. Even were this so, both the local and the general condition, in the case of a large haemothorax, would by this time be very unfavourable. The only alternatives to non-interference are: (1) resection and drainage, and (2) thoracotomy followed by complete closure of the wound.

Non-interference. If the haematoma is very large, it is an immediate danger to life on account of embarrassment to the circulation and respiration. The remote prognosis, too, will be bad, unless it is evacuated, since not only will the expansion of the affected lung be very imperfect, but also because, as is the case with a haematoma in other situations, there will always be the possibility of the occurrence of infection. If, on the other hand, there is little displacement of the heart, and the patient is but slightly distressed, and the temperature settles within a few weeks, it is probably better to rely on spontaneous absorption aided by suitable exercises. It must not be forgotten that neither of the two possible operative measures is free from danger.

Operative interference. A decision as to whether this will be necessary can usually be arrived at by the third week. If operation is considered necessary it should be performed without delay, before the strength of the patient becomes dissipated.

By the middle or end of the third week several aspirations will have proved ineffectual, and the condition of the patient and the size of the haematoma can well be estimated; there will be no firm organization of the clot, the lung will not

be encapsuled by rigid fibrous tissue, and the adhesions binding the mediastinum to the opposite side will still be weak. It must be decided from the condition of the patient whether resection and drainage should be performed or whether an attempt should be made to close the wound completely after thoracotomy. If the latter method is successful, the results, both as regards the immediate prognosis, the length of convalescence, and the ultimate state of the lung, will be infinitely superior to those obtained by the former. If, however, sepsis occurs after thoracotomy and closure, the danger to the patient will be greater than if resection with drainage had been decided upon. It is to be remembered, also, that one is dealing with a patient already exhausted, that there are often superficial wounds near the operation area, and that there is some danger of lighting up latent infection in the clot. If the resistance of the patient seems to be good, it is probably justifiable to perform thoracotomy and to close the wound completely. If, on the other hand, the man appears to have a poor resistance, and especially if there are septic wounds in the operation area, resection and drainage are probably indicated. A very careful study, therefore, of each individual case is necessary before deciding that operative interference is indicated. This should not be undertaken lightly, since the result of converting a sterile into an infected haemothorax is extremely serious. Also, if it is thought that operation is essential, all points of view must be considered before deciding whether resection and drainage or thoracotomy with closure of the wound is to be performed.

Further treatment and course of uninfected haemothorax. It was found to be of the highest importance to allow the patients out of bed as early as possible. When aspiration was done on the seventh or eighth day, the temperature had usually settled by about the tenth day, and the patients were then allowed up for a short time. For the first day a few hours in a chair was sufficient, but on subsequent days the patients were allowed to walk about the ward as much as possible, but were told to rest as soon as they became at all short of breath. In practice, the inclinations of the patients were the best criteria of how much exercise could be taken without undue fatigue and rise of pulse-rate. A rise of temperature up to 101° in the evenings for the first few days after getting up was common, but was not considered an indication for further confinement to bed. Woulff's bottles were tried, but their use seemed to increase the pulse-rate and to cause exhaustion out of proportion to the probable amount of good which they did. Breathing exercises (7) are undoubtedly of great value in restoring the normal movement of the diaphragm and in aiding expansion of the lung. Probably, however, walking, especially uphill, is as or more beneficial. Open-air treatment was employed as much as possible. Up to the time when aspiration could be performed morphia was used freely if the patient was at all uncomfortable or restless, and especially if he was troubled by cough, but after aspiration sedatives or hypnotics were rarely needed.

Condition on transfer to England. Most of the patients were transferred to England about the end of the third week from the wound. By this time they

had been walking about for some days. An X-ray examination was generally made just before they were evacuated. Sometimes it was seen that there was no difference in opacity between the two sides, but usually the diaphragm on the affected side did not have a perfectly sharp outline.

Even in those cases where there was no opacity of the affected side and where the diaphragm was perfectly defined, it was often noticed that its movement on the affected side was greatly impaired or even absent. This condition was found in many patients in whom, except for the fact that they had suffered from haemoptysis and in some cases that a foreign body could be seen with the X-rays, neither the signs nor the other X-ray appearances suggested any intrathoracic injury. It is difficult to see why this fixation of the diaphragm should be so late to disappear, since pain had in most cases passed off some time previously. The physical signs on transfer were either quite normal or consisted of diminished breath sounds with or without some impairment of the percussion note. In the absence of the latter sign, the diminished breath sounds are probably purely the result of the poor diaphragmatic movement. If, however, there is an impaired note to percussion, the abnormal signs are due also to thickening of the pleura owing to deposition of clot. It is said that dyspnoea may persist in some cases, and that it is often functional.

Infected Haemothorax.

These cases numbered thirty-two, of which three were caused by bullet and twenty-nine by shell wounds. Infection occurred in one-third of all the cases of haemothorax. This figure in Rose Bradford and Elliott's series was one-quarter. Of all the varieties of chest injury in patients who reach the Base, septic haemothorax is the most serious, and it is therefore essential to recognize at once the early signs of infections, since time may be as important a factor as in acute abdominal disease. Nearly always the general appearance of the patient is the most reliable indication of the onset of sepsis, but in a few instances the infection was only discovered by the routine bacteriological examination of the fluid, the typical septic appearance never being acquired. It must be emphasized, however, that not only should the fluid be examined at once if there are any signs suggestive of infection, but also that resection should under no circumstances be performed in the absence of bacteriological evidence, even though from the signs and symptoms it appears almost certain that the haemothorax is infected.

Signs and symptoms of infected cases. All grades of infection were seen, and many patients did not show all of the signs and symptoms described below. An infected patient does not improve at a steady rate like an uninfected one, and, in fact, Rose Bradford says that any case not definitely improving by the fourth day should be suspected of being infected. In the less virulent varieties the general condition remained stationary or deteriorated at a slow rate, although in a few instances there was a slow but uninterrupted improvement; the

comparative slowness of this latter, however, generally gave one the clue that the case was certainly, though mildly, infected. In estimating the rate of improvement, the general appearance of the patient, his sleep, and appetite must all be taken into account as well as the temperature and the pulse-rate. In septic patients, sleep was difficult to obtain, appetite was bad, and any pain present was made worse by meals. Pallor, which was never a feature in uninfected cases, was often found to be an early and valuable sign of the onset of sepsis. Pain and tenderness of the affected side and dyspnoea and cyanosis were usually out of all proportion to the amount of fluid present. The most distinctive sign, however, of an infected haemothorax is the early and often extraordinarily rapid wasting; in no other situation does sepsis bring about such a rapid loss of flesh. This, in the worst cases, together with cyanosis of the lips, furred tongue, cold and clammy extremities, perspiration, and general appearance of exhaustion, makes up an unmistakable picture. The temperature is of little assistance, since, even with severe infection, it was sometimes quite low. The pulse was a more valuable guide, and, unless there are complications or there is a very large effusion, sepsis should be strongly suspected if the pulse-rate is persistently over 100. Occasionally a pulse of only 80 was found in patients suffering from obvious and virulent sepsis, but this was most unusual.

The mental condition was generally very depressed, and the patients realized the gravity of their illness. It is said to be a characteristic feature of infection by gas-forming organisms for the mental state to remain bright, and for the man to be cheerful in spite of the fact that he is *in extremis*. This was seen here in one instance. The patient was admitted with a septic haemothorax; he was very dyspnoeic and cyanosed; the temperature was 104° and the pulse 140. He remained perfectly cheerful up to the time of death, which occurred suddenly on the following morning, and he never realized that he was in any way dangerously ill. At the autopsy all the organs showed very striking changes due to gas-producing organisms.

The chest fills up after aspiration and needs repeated emptyings, and it is said that a sudden filling up may be the first sign of infection. It is doubtful if this is a secondary haemorrhage or an acute inflammatory effusion. This happened once here, and unfortunately a diagnosis of a secondary haemorrhage was made and operation was postponed. The patient ultimately died, although resection was only delayed for two days.

The nature of the fluid in infected cases. Often there is no difference between the appearance of septic and sterile fluids. It is said that a carmine tint of the froth denotes haemolysis and sepsis, but, as stated before, this is also seen sometimes in non-infected fluids and therefore cannot be taken as infallible evidence. A foul smell, of course, was certain evidence of infection and was an indication for immediate resection.

Microscopic appearance and bacteriology of infected fluids. Leishman's or thionin blue were found to be the best stains. The red cells and the leucocytes tended to degenerate early. The number of organisms seen in a film was

subject to considerable variations. In some cases a prolonged search for them was necessary, and in others countless numbers were to be seen in a single field.

In the more chronic infections the organisms were mainly intracellular. As a rule it was always possible to see organisms in a film preparation when subsequent culture showed that they were present; an opinion therefore could at once be formed from their numbers and type as to whether immediate resection was necessary. In every case, however, a sample was sent to the bacteriologist and reports as to the results of aerobic and anaerobic culture obtained. The commonest infecting organisms were streptococci, pneumococci, and Bacillus perfringens (Bac. aerogenes encapsulatus). Bacillus coli was found in a few instances. Mixed infections were common, usually streptococci and Bacillus perfringens. It was often impossible to distinguish without the help of cultures between pneumococci and streptococci.

Elliott and Henry (13) find that it is not unusual for anaerobes to be occluded in clot, so that the fluid is at first reported sterile, and that a sample drawn off later is found to be infected. This also was noticed here in several instances. They find that this takes place far more often with anaerobic than with other infections. In 101 cases investigated by them the infecting agents were as follows:

Pneumococci	17
Streptococci and staphylococci	38
Anaerobic bacilli alone	23
„ „ with other organisms	42
Coliform bacilli and diphtheroids	4

Of the anaerobic infections they find that most are due to Bac. perfringens. This was also the experience in our cases.

Types of septic cases. Patients suffering from all grades of infection were seen, from those in whom the sepsis was unsuspected and discovered only by means of the routine bacteriological examination, to those with obvious and virulent infection and who were almost beyond the stage for operation when they were admitted.

1. *Patients with very mild infection.* There were several whose clinical course was as, or in a few instances more, favourable than that of the majority of uninfected ones. In these, as said before, the discovery of organisms might be the only sign of infection. Usually, however, the temperature was more persistent and repeated aspirations were found necessary. This class will be referred to again later, when the question of their treatment is discussed.

2. *Patients who at first progressed satisfactorily and were thought to be uninfected, but showed signs and symptoms of infection about the fifth or sixth day.* The majority of the cases were of this variety. In these, the most valuable diagnostic sign was the gradual deterioration in the general condition. The pulse-rate at first often showed no rise and the temperature was of little

assistance in diagnosis. Generally slight dyspnoea and cyanosis, especially of the lips, came into evidence, and the man began to lose his appetite, to sleep badly, and to complain of pleural pain. Sweating was a common and very valuable sign. Generally loss of weight was noticed, but the patients rarely reached the stage of profound and obvious sepsis, since the infection was less virulent than that which showed itself in the first few days, and also because facilities for bacteriological examination enabled an early diagnosis to be made.

3. *Patients admitted with signs of severe and obvious infection.* In these the infection was very acute and had developed rapidly during the journey. The pulse-rate was almost invariably over 100, generally 120–30; the temperature varied, being occasionally below 100°, but was usually 102–4°. The appearance of the patients was typical, and has been described when the differential diagnosis between a septic and a sterile haemothorax was discussed.

This class of case was largely made up of patients with gaping wounds of the pleura and of those with a haemothorax complicated by pneumonia on the opposite side.

Treatment of infected haemothorax. As said before, an early diagnosis as to the presence and degree of infection is essential. The methods of treatment at one's disposal are (*a*) immediate resection; (*b*) preliminary aspiration followed by drainage; and (*c*) aspiration only.

At first it was thought necessary to perform resection directly the presence of infection had been diagnosed and before the general condition could deteriorate, and that delay was unjustifiable.

Further experience, however, showed that there were many factors, which will be referred to later, to be considered, and that immediate resection was not indicated for every case of infected haemothorax.

The general conclusion arrived at was that for the majority of cases immediate resection was necessary, but that in others a much better result could be obtained by aspiration. In our experience, however, preliminary aspiration for patients in whose case it is certain that resection will ultimately be necessary has no place as a method of treatment. This opinion is not a general one and will again be referred to.

(*a*) *Immediate drainage.* This is indicated if the infection is gaining the upper hand, as evidenced by the progressive deterioration in the general condition of the patient and by the acceleration of the pulse. It should not be delayed, too, if the fluid is foul or if film prepared from it shows that many organisms (other than pneumococci) are present, even though the patient may not be seriously distressed. Even the worst cases stood the actual operation well, and, except when there was already a gaping wound into the pleural cavity, or when there was much bronchopneumonia or purulent bronchitis, the immediate relief to the patient and the general improvement, as shown by the slowing of the pulse-rate and the fall of temperature, were highly satisfactory and infinitely greater than would have been obtained by aspiration.

The class of case which is liable to give rise to the greatest difficulty and anxiety in coming to a decision as to whether aspiration or resection is to be performed is the one where there is an infection of the haemothorax by pneumococci. If it is certain that these are the only infecting organisms, there is little doubt that aspiration will give the better result. Unfortunately, however, it is often impossible, without the help of cultures, to distinguish pneumococci from streptococci, and, since such patients are usually seriously ill, it is generally unsafe to delay resection until the results of the cultures are known, because, in cases of severe and acute infection, time is certainly as important a factor as in acute abdominal conditions.

The following two cases illustrate the dangers of resection and the efficiency of aspiration when there is a pure pneumococcal infection of the haemothorax. Both these patients were admitted within a few days of each other and were fairly comparable.

The first man admitted had been wounded about six days previously. He was very distressed and cyanosed and sweated profusely. The pulse was poor and averaged 110; the temperature was 101°. His general appearance suggested obvious and virulent sepsis. Examination showed that there was a large haemothorax on the right side and pneumonia of the lower lobe on the left side. The haemothorax was explored and a stained film prepared. Gram-positive cocci were seen, some in pairs and others in short chains. Other organisms appeared as short Gram-positive rods. The majority of the organisms were not typical pneumococci. The sputum was not 'rusty', but was stained with bright blood. In view of the uncertainty from the film appearances as to the nature of the infection and the fact that the man was so ill, it seemed unjustifiable to delay resection. This was done, therefore, a few hours after admission, and its immediate effect left little to be desired. At the operation the lung expanded well, and for a few days the patient progressed satisfactorily. The pulse-rate fell to about 80 and the temperature did not rise above 100°. By this time the sputum had become typically 'rusty' and examined microscopically showed pneumococci in large numbers, and the culture report on the haemothorax fluid that pneumococci only were present was received. On the onset of secondary infection, a few days after the operation, the patient began to relapse. He again suffered from pain and dyspnoea; the temperature and pulse-rate rose and the cyanosis reappeared. These symptoms gradually became worse and were found to be associated with progressively increasing collapse of the right lung. He remained in a dangerous state for some weeks and then very slowly began to improve. When he was transferred to England, about two months after the operation, he was still in a very weak and wasted condition and there was a large cavity which required drainage.

The second patient was admitted soon after the first. The history was that he had been wounded twelve days previously. He also had suffered from a large haemothorax on one side and pneumonia on the other. Pneumococci had been found in the haemothorax fluid, and in his case treatment had consisted in aspirating the haemothorax on the sixth day after the wound, 48 oz. being drawn off. A few ounces of turbid fluid, which later on developed on the pneumonic side and which contained pneumococci in pure culture, had also been aspirated. On admission here, his temperature and pulse were normal. Resolution was progressing well in the pneumonic lung and the abnormal signs on the side of the haemothorax had almost completely disappeared, and no opacity could be seen with the X-rays. In a few days he was walking about the ward and convalescence was well advanced.

(*b*) *Aspiration as a preliminary to resection.* In favour of this it might be supposed that the patient would be prepared for the operation of resecting, aspiration having been sufficient to relieve the symptoms and temporarily to check the sepsis, and that the ultimate expansion of the lung would be better than if resection had been performed at once.

It is said, too, that if a large effusion is suddenly removed, as by resection, there is a danger of acute oedema of the lung supervening. This is probably a rare occurrence. In one case in this series there was a large effusion grossly infected by streptococci. The patient was obviously extremely ill, and resection was done within an hour of his admission. The immediate result was excellent, the patient recovering from the anaesthetic with a strong and regular pulse of 80. He passed a good night, but collapsed somewhat suddenly early the next morning, became dyspnoeic and cyanosed, and died a few hours later. This collapse did not take place until about twelve hours after the operation. At the autopsy it was seen that both lungs were extremely oedematous and congested. The spleen was large and soft, and death was certainly due to sepsis. In view of the late onset of the oedema it is probable that this was a terminal phenomenon caused by acute cardiac failure rather than by the sudden removal of a large haemothorax.

In our experience, it was found that the patients stood the actual operation of resection very well, that the immediate effect of resection was infinitely superior to that produced by aspiration, which often made but little immediate difference to the general condition of an acutely septic patient, and that the secondary deterioration in the general condition and the amount of collapse of the lung were not lessened in those particular patients for whom a preliminary aspiration had been done. In view, therefore, of the rapid rate at which a severely infected case deteriorates, it does not appear probable that the theoretical advantages of a preliminary aspiration outweigh the danger occasioned by the loss of valuable time entailed by its employment. If, however, it is doubtful whether resection will ultimately be necessary, these objections do not apply.

(*c*) *Aspiration.* It might be considered unjustifiable to run the risk of leaving a patient with a closed infection, but experience has shown that many excellent results have been obtained by aspiration only. The patients chosen for this method of treatment should be either those in whom the bacteriological evidence is the only indication of infection or those in whom the infection is not virulent, as is shown by the general condition either remaining stationary or slowly improving. If under these circumstances a close and careful watch is kept, it seems rational to try the effect of aspiration. If this proves successful, the patient will be spared the acute illness and the slow convalescence associated with resection, and the ultimate state of the lung is likely to be infinitely better.

It is sometimes difficult to decide whether aspiration should be given a trial, owing to the uncertainty as to how much of the distress is caused mechanically

and how much by sepsis. The quantity of fluid must be taken into account and also the number and type of the organisms seen in the film preparation. If the effusion is small, the organisms numerous, and the leucocytes degenerated, it is probable that the case is not a suitable one for aspiration even though the patient may not seem very ill. If, on the other hand, there is a large amount of fluid, the organisms few, and especially if the infection is purely pneumococcal, it is likely that the mechanical factor is the important one and that aspiration will be successful.

The view that in some cases a better result will be obtained by aspiration as opposed to resection is held by R. D. Rudolf (1) but not by Rose Bradford and Elliott (2), who say that very nearly all patients with an infected haemothorax which has been treated only by aspiration ultimately need resection. They state that possibly it may be justifiable to give aspiration a trial if the infecting agents are the pneumococcus, M. tetragenus, or diphtheroid bacilli, but not if it is streptococcus, staphylococcus, B. influenzae, or anaerobic bacilli.

In none of the cases, however, in our series, for which aspiration had been performed instead of resection, was the latter found necessary. All these patients were under observation until the temperature had definitely settled, and at the time of their transfer there were no signs, local or general, to indicate that in the future further operative procedures would be needed.

The infected patients in this series who were treated by aspiration and not by resection numbered six.

Case I. A few streptococci in short chains were seen in the film prepared from the fluid and were also found by culture. Apart from this the patient had been considered to be uninfected. The effusion did not reach higher than the inferior angle of the scapula. The temperature settled by the end of a fortnight and the abnormal signs disappeared spontaneously.

Case II. On this occasion also the diagnosis of sepsis would not have been made except for the routine bacteriological examination, which revealed the presence of B. aerogenes encapsulatus. One aspiration only was necessary, 20 oz. of fluid being drawn off. In this patient a pericardial rub developed just before the aspiration on the sixth day, but persisted for two days only and gave rise to no symptoms or acceleration of the pulse-rate, which at no time rose above 84. At the end of ten days the temperature had settled and the man was walking about, by which time the abnormal signs had almost disappeared and the X-ray appearance was normal, except for some loss of movement of the diaphragm on the affected side.

Case III. Streptococcus and B. aerogenes encapsulatus were present in small numbers. Although repeated aspirations were necessary and the temperature did not finally settle for four or five weeks, and the patient became somewhat anaemic, the chest signs disappeared satisfactorily, and there is little doubt that the result was infinitely better than would have been obtained by resection. This patient was, of course, closely watched, and although improvement was very slow and sometimes stationary, there was never any deterioration in his condition. The pulse-rate averaged 96–110.

Case IV. This man was admitted ten days after the wound; he was very pale and looked ill. The pulse-rate, however, was only 96 and the temperature

101°. The signs and X-ray appearance showed that there was a pericardial effusion and a small haemothorax on the right side. The haemothorax was aspirated, 10 oz. being drawn off. Examined bacteriologically, the fluid was found to contain streptococci. Although there was an evening rise of temperature to 99° or 100° for nearly six weeks, the general condition steadily improved and the abnormal signs disappeared. (Case V in Appendix.)

Case V. There was a large haemothorax slightly infected with a Gram-negative bacillus. Aspiration was done first on the sixth day, also on the seventh and ninth, three and a half pints altogether being removed. The patient never acquired the typical appearance associated with sepsis, and recovery, both as regards the local and the general condition, was perfect. The temperature had settled and he was walking about by the tenth day after the wound. The X-ray examination made just before he was transferred to England showed no opacity on the affected side.

Choice of anaesthetic. At first a local anaesthetic was used as a routine, and, unless contra-indicated by the presence of much bronchitis, a preliminary injection of morphia, gr. $\frac{1}{6}$–$\frac{1}{4}$, was given half an hour beforehand. It was found that the respiration was better when the patients lay on the sound side. As regards abolishing the pain of the operation itself the local anaesthesia was very satisfactory, except that sometimes there was difficulty in obtaining good anaesthesia just while the periosteum was being stripped from the posterior surface of the rib.

It was found, however, that there was more shock and strain on the heart with local than with general anaesthesia, owing to cough and pleural irritation while the fluid was being evacuated. In a nervous patient, too, the fear and discomfort entailed by an operation of this kind while he is conscious must be injurious.

When a light chloroform anaesthesia was used the patients stood the anaesthetic and operation exceedingly well, and if, soon after the operation was finished, a small dose of morphia was given, they came round without much discomfort and the troublesome and painful cough did not occur.

It appeared, therefore, that this general anaesthesia was better than the local method, and that the only real contra-indication would be the presence of severe bronchitis.

Position of the opening. As is pointed out in a *Memorandum on Treatment of Injuries in War*, issued by the War Office (4), the diaphragm is sometimes in an abnormally high position, so that care must be taken not to make the opening too low. The X-rays and preliminary needling, however, should be a guard against this. This position of the diaphragm has been considered earlier.

If the original wound is low down, it may be enlarged and the rib resected at this situation, provided that dependent drainage will be secured. If, however, there is any doubt about the latter point, another opening must be made in a suitable position. Generally the rib chosen was the ninth, just behind the posterior axillary line. A large drainage-tube was inserted, but irrigation at the time of the operation was rarely resorted to. It was found that there was no advantage in keeping any second wound that might be present open for the

purpose of irrigation. No such second opening, therefore, was made. It is essential for the opening to be made into the very lowest part of the cavity. Openings forward in the axilla do not give satisfactory drainage.

Retention of metal. This is far commoner with shell than with bullet wounds, and partly accounts for the increased frequence of infection in haemothorax caused by the former class of missile. Since, however, it is probably unwise to remove the foreign body before it has had time to give rise to infection, and since abscess of the lung is very rare both in the early and late stages, it would seem that indications for removing metal would seldom arise.

Probably the usual position of retained fragments is the pleural cavity or the parietes, since the lung offers very little obstruction to their progress. In one case a piece of shell was removed from the lung before admission to this hospital on account of severe and repeated haemoptysis.

After-treatment and course of infected haemothorax. Before certain precautions were taken to prevent secondary infection it was invariably found that, although the immediate effect of resection might have left little to be desired, the improvement was not maintained. After a few days the temperature and pulse-rate again rose, breathlessness and cyanosis returned, and wasting continued. Often the condition of the patient was worse than before operation, and this persisted for several weeks. This deterioration was found to be associated with a secondary infection, mainly streptococcal, and the lung became progressively more collapsed. In the case of pneumococcal empyema of civil life secondary infections also occur, but do not seem to have a similar deleterious effect. The reason for the difference between the course of infected haemothorax and pneumococcal empyema is possibly to be explained by the fact that in the latter variety the disease has spread from the lung to the pleural cavity, so that there is considerable thickening of the pleura, which forms a barrier of defence. Also the whole pleural cavity is less often involved than is the case with infected haemothorax. Possibly, too, if there is a laceration of the lung, the infective process in it may be heightened by the increased movement consequent to drainage.

Methods adopted to prevent secondary infection. (1) The employment of a long drainage-tube leading to a receptacle containing an antiseptic solution below the level of the bed. The main advantage is that the outer dressings do not become soiled, so that 'packing', a most prolific source of secondary infection, is never necessary. Further advantages are that should irrigation of the cavity be deemed advisable, this can be done as often as every two hours with no disturbance to the patient, and also that a suction action is produced which aids re-expansion of the lung. After four or five days the long tube is replaced by one of the usual length, by which time the amount of discharge is small enough to be absorbed by the dressings. (2) The employment of a sufficient number of sterilized pads to ensure that the outside one is never stained, no unsterilized wool being used. At the daily dressings all manipulations are performed

entirely with sterile forceps. (3) The Carrel-Dakin method (8) is applied in order to keep the inner dressings constantly moist with hypochlorite solution. The practice here is to use a Carrel tube in the form of a horseshoe with multiple small perforations. This is retained in position by being placed under the safety-pin on the drainage-tube and by being attached to the skin higher up with strapping. The open ends are connected with the tube leading to the reservoir by means of a two-way glass connexion. Irrigation with a few ounces of hypochlorite is carried out every two hours. Only when the discharge is very small in amount is it necessary to protect the surrounding skin with sterile vaseline, since the irritating quality of the hypochlorite is almost instantaneously destroyed by contact with pus. It will be noted that the fluid is not introduced into the pleural cavity, but that the object aimed at is to prevent constant reinfections owing to infective matter being sucked back.

Results gained by the adoption of the above methods. In the majority of patients the after course was rendered as favourable as that of a pneumococcal empyema, the improvement after resection being steadily maintained. It was particularly noticed that the wasting ceased and the typical 'septic' appearance was lost. In a few patients, however, the effect of resection was disappointing, and their condition remained serious for several weeks in spite of the fact that the state of the empyema cavity was satisfactory. In these cases their condition was due to bronchopneumonia or purulent bronchitis.

Importance of bacteriological control. If the condition of the patient is unsatisfactory, attempts to improve drainage or to remove foreign bodies will not be followed by improvement if smears taken from the pleural cavity show a low degree of infection (less than five organisms per field). Under such circumstances some other cause, usually bronchitis or bronchopneumonia, is responsible for the bad progress. If, on the other hand, the smears after about ten days still show a large number of organisms, some local cause should be sought. Usually the drainage opening is too small or is placed too high in the cavity. It is claimed that when a low degree of infection has been attained the opening may be closed by suture, even although there may still be a large cavity. It has never been found possible to do this here, although the expansion of the lung has been definitely aided by blocking the opening for a week or ten days. This is most conveniently done by tying off the end of the drainage-tube.

Irrigation of the cavity. This was performed only if much adherent clot was found at the operation, or if the discharge was very grossly contaminated with organisms or was foul. Under these circumstances irrigation every two or four hours with a pint of hypertonic saline solution for a few days is of great value. By its means elimination of dead tissue, i.e. clot, is hastened so that spontaneous sterilization can proceed. In the absence of the above indications, irrigation of the cavity was found to cause the temperature to persist and to hinder the natural defences. Several patients were admitted in whose case irrigation with various fluids had been carried out regularly. On admission smears from the pleural cavity showed an infinite number of organisms, but in every case, when

irrigation was discontinued and precautions to prevent reinfection taken, the smears showed less than five organisms per field after about ten days.

It appears that the risk of secondary haemorrhage after resection is slight. In one case only in this series did this occur. Here there was a very virulent infection which led to a fatal termination. At the autopsy it was seen that there was an extensive laceration of the lung, the affected part of which was in a semi-gangrenous condition.

Open-air treatment was used whenever practicable, and it was found to be of the highest importance to allow the patients out of bed as soon as possible. This was generally done even before the temperature had quite settled. The pulse-rate sometimes remained above 100 for some weeks, but if sitting up in a chair for part of the day did not cause it to rise much above this, it was not taken as an indication for further rest in bed. It was found that directly the patients began to get up their appetite improved, and, more important, sleep returned and the expansion of the lung was aided. It must be remembered that the displacement of the mediastinum sometimes does not right itself for some weeks, so that, in the absence of other abnormal signs, the patient should not be confined to bed for an unnecessarily long period on the supposition that the abnormal position of the apex beat is evidence of a dilated heart. The absence of bruits, the small difference in the pulse-rate between lying down and sitting up, and the X-ray appearance are the most reliable indications.

Two patients in this series developed 'indigestion' soon after resection. This persisted and was still present when they were transferred to England. There was no vomiting, but they complained of pain, which came on a few minutes after each meal and lasted for an hour or so. Possibly the pain, under these circumstances, is due to the pulling on diaphragmatic adhesions by the filling up and movements of the stomach. The absence of vomiting makes it improbable that the condition is due to acute ulceration of septic origin.

If the pain is due to adhesions, one would expect that it would be alleviated by appropriate exercises and movements when the patient is in a condition for these to be employed.

As regards drugs, it was always necessary to give hypnotics freely in order to obtain sleep, and, as a rule, to continue them until the patient could leave his bed for part of the day. Morphia, heroin, hyoscine, tinct. opii, and Dover's powder were all useful, but in some patients this lack of sleep proved very intractable, and was the most troublesome symptom to treat. Digitalis was tried in order to combat the rapid pulse, but was quite useless even in full doses. Constipation was usually easily dealt with. If there was much discomfort from distension, pituitary extract was often extraordinarily efficacious, producing its action sometimes in less than a minute. The most satisfactory method of controlling diarrhoea, if it occurred, was Dover's powder gr. v every two hours as long as necessary. If there was coincident bronchitis, an expectorant mixture containing ammonium carbonate and potassium iodide was given, and in cases where the expectoration was foul the inhalation of tinct. benzoini co.

was of value. Even when there is much bronchitis, morphia is of great value in allaying breathlessness and in slowing the pulses.

Alcohol, in the form of brandy or champagne, was given freely if the patient liked it. Strychnine, camphor, and pituitary extract were used as 'stimulants' when indicated, but (with the exception possibly of the last named) none seemed to be of great value. During convalescence cod-liver oil was certainly beneficial, but if given too soon always caused nausea and impaired the appetite. Vaccine treatment unfortunately was not made use of, but probably in some cases would be of great value, especially if the temperature was being kept up by broncho-pneumonia.

The treatment of infected patients for whom aspiration and not resection had been done did not differ from that of uninfected ones, except that more frequent aspirations might be necessary and that a very close watch had to be kept for any signs which might indicate that the infection was getting the better of the patient.

Immediate prognosis of infected haemothorax. We have no statistics as to how many patients with chest wounds die before reaching the Base. Presumably, however, the fatal result in the majority of these would be from haemorrhage and shock, and not from sepsis. In the 129 cases of chest wounds considered here, there were 11 deaths. Of these, 7 were due to a septic haemothorax, the mortality in this latter class of case being 21·9 per cent.[3] The factors to be considered in forming a prognosis are:

(*a*) Gaping wounds allowing the exit of pus and the entry of air with the respirations carry a very bad prognosis. There were three such patients, none of whom recovered.

(*b*) The earlier the sepsis manifests itself after the wound the worse is the prognosis.

(*c*) The time elapsing between the onset of sepsis and resection is probably the chief factor in, at any rate, the immediate prognosis.

(*d*) The virulence and type of infection is a great factor in determining the amount of collapse of the lung and the density of the adhesions, even more than the time elapsing before draining is established. In some of the patients with an excessive amount of collapse of the lung, resection had been performed in the first week after the wound.

(*e*) Only one of the four patients with a haemothorax complicated by pneumococcal lobar pneumonia died, although all were in a very critical condition.

(*f*) The immediate and remote prognosis when resection can be replaced by aspiration is almost as good as that of an uninfected case.

(*g*) Rose Bradford and Elliott (2) find that the prognosis of streptococcal is worse than that of anaerobic infections.

[3] Since precautions against secondary infection have been taken, there have been twenty-six cases of uncomplicated infected haemothorax under treatment (including patients admitted after the completion of this paper). Out of these there have been three deaths. This lowered mortality is attributed almost entirely to the above-mentioned precaution.

Both the time and mode of transfer to the Base are of importance. Owing to the extreme need for rest in the early stages, most patients are not transferred to the Base until after the third day from their wound. Although transit by barge is infinitely more comfortable than the train journey, it suffers from the great disadvantage that it may take several days, during which time there are no facilities for bacteriological or surgical work, and this delay may be a very great disadvantage and danger to infected cases, because if the sepsis manifests itself early it is usually very acute and virulent.

Ultimate prognosis of infected haemothorax. Unfortunately only a limited part of the course of these cases was seen. Nothing, therefore, can be said as to when the sinus closes in the majority of cases, although it is stated (4) that most do so in two to four months.

Apparently the number needing Estlander or decortication operations is not a large one. It is to be seen whether the general health of these patients is good or whether incomplete lung expansion, persistent sinus, chronic bronchitis, and possibly bronchiectasis or tuberculosis are common after-effects. The comparative rarity of abscess of the lung has already been referred to, and possibly one may infer from this that retention of metal is not of great importance.

Abdomino-thoracic Wounds and Injuries.

Patients suffering from abdomino-thoracic injuries were less numerous than would have been expected. This was possibly due to the fact that many had died in the early stages. The number seen here was four. Of these, three were the result of wounds and one of crushing injury.

1. *Cholohaemothorax.* There was a discharge of bile through the resection opening, which had been made at the site of the original wound. At the operation for draining the empyema it was found that there was a superficial laceration of the upper surface of the liver. This condition persisted for some weeks, but when the patient was transferred to England the discharge of bile had ceased. There was no subdiaphragmatic abscess.

2. *Perforation of abdominal aorta.* There was a small haemothorax and death took place three weeks after the wound. It was found at the autopsy that death was due to a large infected retroperitoneal haematoma produced by a double perforation of the abdominal aorta. (Case II in Appendix.)

3. *This patient had a small haemothorax and marked abdominal symptoms.* When the latter quieted down a pulsating tumour was felt on the right side of the epigastric region. It was thought that this tumour was probably a traumatic aneurysm. There was a large wound deeply lacerating the back muscles, and the man had also suffered from 'spinal concussion'. The patient made a good recovery.

4. *Retroperitoneal haematoma and contusion of the kidneys.* This man had been injured by part of a parapet falling on him. There was a sterile

haemothorax complicated by abdominal symptoms and haematuria. The patient died on the day of admission, about seven days after the injury, and at the autopsy it was found that there was a small haemothorax, a large retroperitoneal haematoma, and contusion of the kidneys. The liver was in an advanced stage of typical alcoholic cirrhosis.

Subdiaphragmatic abscess. Contrary to what one might expect, this does not seem to be a common complication, and no instances occurred in this series.

Diaphragmatic hernia. This was suspected in one patient with a sterile haemothorax. The man made an excellent recovery after aspiration, but when he was X-rayed, just before he was transferred, a curious condition was seen. Instead of the normal curve of the diaphragm, there was a conical protrusion interrupting it. The line of the diaphragm and of this protrusion was well defined, and it was thought that there must have been a laceration of the diaphragm with some protrusion of the liver or of a subdiaphragmatic haematoma. No foreign body could be seen. There were, however, no symptoms and the patient was transferred to England *in statu quo*.

Total Mortality.

Statistics as to mortality are of little value, since they would vary enormously according to the time when the cases were under treatment. In the French army in the Crimean War the mortality is said to have been 90 per cent. (10). In the Spanish-American War it was 27·5, and in the South African War 14 per cent.

The number of deaths from all causes in this series of 129 was 11, i.e. 8·5 per cent. Of the fatal cases, death was due to septic haemothorax in 7, to perforation of the first part of the aorta in 1, to pneumococcal pneumonia in 1, and to abdominal complications in 2 cases.

The mortality for infected haemothorax was 21·9 per cent.

In Rose Bradford and Elliott's (2) series of 450 cases the total death-rate was 10 per cent., of which 70 per cent. was due to septic haemothorax. In the 117 cases of the latter there were 36 deaths due to sepsis.

Early Prophylactic Operations for the Prevention of Sepsis.

This subject has come into prominence lately, and some reference must be made to it on account of its extreme importance. In this connexion a recent paper by Elliott (15) deserves careful study. He concludes that such operations should be performed for certain selected cases only, the indications being:

1. *The presence of a gaping wound, too large to close spontaneously, into the pleural cavity.* He states that in these cases excellent results are being obtained by early closure, whereas if this is not done the results are uniformly bad.

2. *Tangential wounds with much laceration of muscle, rib, and possibly pleura and lung.* If such wounds are not cleansed, sepsis of a virulent nature is liable to develop.

As regards the presence of foreign bodies of large size, he states that in such cases very severe infection almost invariably occurs, but that 'it remains for surgery to prove whether expectant treatment or immediate attempts to cleanse the wound in chest and lung more or less completely by early operation will yield a lower death-rate'.

For other cases he opposes early prophylactic operation for the following reasons: (1) That only about 25 per cent. of all cases ultimately become infected, and that of these many will present one or other of the above indications for operation. (2) That mere retention of *small* foreign bodies predisposes neither to an especially severe form of infection should sepsis occur, nor to any incapacity in sterile cases.

Although the patients were admitted here too long after their wound for prophylactic operation to be contemplated, an opinion as to the value of the latter could be formed. The experience here was such as to confirm entirely the views of Col. Elliott, both as to the indications for operation and as to the undesirability of surgical interference as a routine procedure. This opinion is based on the results in a large number of patients treated by expectant methods, and also in a very limited number of those treated by early operation. In many of the latter, however, some of the dangers of early operation were demonstrated.

Additional reasons against routine operation, in the absence of the indications mentioned by Elliott (15), are the following: (1) That an anaesthetic is strongly contra-indicated during the first few days after a chest wound on account of shock and the danger of fresh haemorrhage due to straining. Further, there is increased risk of such complications as bronchitis, pneumonia, and massive collapse, since, even before the anaesthetic, the tubes contain an excess of mucus and blood. (2) The danger of infection spreading to the pleural cavity. (3) That a moderately small opening into the pleural cavity rapidly becomes firmly sealed, so that superficial sepsis, even if it occurs, can then be efficiently treated without risk of infection being carried through to the pleura. (4) The relatively good prognosis of infected haemothorax, if the above-mentioned indications for early operations are absent, provided that an early diagnosis of infection is made.

Conclusions.

The following are some of the main points brought out by the experience gained from this series of cases:

1. If a haemothorax has been produced by a bullet wound it is very improbable that sepsis will occur. Of those produced by shell wounds about half are infected.

2. Many patients with penetrating wounds, both bullet and shell, when seen at the end of a week, show no signs of lung injury.

3. Pain and, more important, tenderness and hyperaesthesia of the skin in a case of haemothorax should make one strongly suspect that there is infection.

4. Cyanosis and dyspnoea generally mean that there is infection of a haemothorax unless the latter is a very large one, but of all the early symptoms of infection, sleeplessness is perhaps the most valuable.

5. The loss of weight occasioned by a septic haemothorax is a striking feature and in excess of and more rapid than that produced by sepsis in other situations.

6. Lobar pneumonia complicating a haemothorax is not as serious as might have been expected.

7. Contrary to expectation, abscess of the lung is a rarity.

8. Bronchial breathing is often heard over a haemothorax. The most valuable signs for the differential diagnosis between a haemothorax and pneumonia are the degree of impairment of the percussion note and the presence or absence of râles.

9. The X-rays are essential for the diagnosis and treatment of haemothorax.

10. After shock has subsided pallor is not seen in patients suffering from even a large haemothorax if it is sterile.

11. A haemothorax, if of moderate size, should be aspirated after six or seven days, and no harm will result if this is done as a routine for every haemothorax.

12. Clotting to a degree sufficient to prevent efficient aspiration of a haemothorax is rare.

13. Secondary haemorrhages after the first few days do not occur in sterile cases.

14. The position of the diaphragm is often abnormally high in cases of haemothorax, and this fact is to be remembered when aspiration or resection is performed.

15. It is rare for organisms to be found by culture in a haemothorax fluid if they cannot be seen in a stained film prepared from the fluid.

16. Resection is not indicated for every case of infected haemothorax. The bacteriology, general condition of the patient, and the size of the haemothorax must all be taken into account in coming to a conclusion as to whether resection or aspiration should be done.

17. The advantages of preliminary aspiration when it is certain that resection will be necessary are overbalanced by the loss of valuable time entailed by this procedure.

18. When a haemothorax is infected solely by pneumococci, a better result will probably be obtained by aspiration than by resection.

19. The Carrel-Dakin method applied to the treatment of septic haemothorax

after resection will prove to be of the very highest importance and value, since by its means secondary infection, which is one of the chief dangers of this class of case, can be almost completely eliminated.

20. For resection a light chloroform anaesthesia is generally safer than, and preferable to, a local one.

21. Cases where there is a gaping wound into the pleural cavity carry a very bad prognosis.

22. The virulence of the infection rather than the time before drainage is established determines the density of the walls of the empyema cavity and the amount of collapse of the lung in cases of septic haemothorax.

23. It is of great importance to get patients for whom resection has been done out of bed for a few hours at the earliest possible date, when the general condition and the pulse-rate allows.

24. The displacement of the mediastinum may take a considerable time to right itself, even after operation, so that care must be taken not to mistake the abnormal position of the apex beat as evidence of a dilated heart.

25. Bronchial breathing, râles, and an impaired resonance at the left base may be the only signs of even a large pericardial effusion.

26. The rarity of subdiaphragmatic abscess is somewhat surprising.

27. By far the commonest cause of death in cases of chest wound which reach the Base is sepsis occurring in a haemothorax.

28. A lower mortality in infected cases is to be gained by earlier diagnosis and more efficient treatment of sepsis, rather than by early prophylactic operations undertaken as a routine.

APPENDIX

Notes on Cases.

Case I. Simple fracture of ribs causing a pneumo-haemopericardium.

The patient, Lance-Corporal B., aged 23, was admitted on August 6. The history was that two days previously a weight had fallen on his back while he was leaning forwards.

On admission, the temperature was 100°, pulse 80. He was dyspnoeic and cyanosed, and both lungs were oedematous. He was given injectio atropinae, gr. $\frac{1}{50}$. An examination was made about an hour afterwards and it was found that the lung oedema had completely disappeared. The apex beat could not be felt and the cardiac dullness could not be mapped out. There were no signs of a pneumothorax, but there was a loud splashing heard over the cardiac area. This synchronized with the heart-beat and was clearly heard by the patient, who by this time felt perfectly comfortable. He was given an injection of morphia, gr. $\frac{1}{4}$, and passed a very good night until about 4 a.m., when he again became dyspnoeic. The lungs were again found to be oedematous, but the condition was relieved almost instantaneously by another injection of atropin ($\frac{1}{100}$). He was again dyspnoeic at about 10 a.m. An X-ray examination showed that the cardiac opacity was enlarged to right and left, but that

there was a definite clear area in it. The chest, apart from the cardiac opacity, was quite clear

A needle was put into the pericardium and 10 ounces of blood and a considerable quantity of air were drawn off. The pleural cavity had been needled from behind, but with a negative result. The patient was much relieved and, except that for a few days he suffered from occasional acute attacks of dyspnoea due to pulmonary oedema, which were immediately relieved by injectio atropinae, gr. $\frac{1}{100}$ p.r.n., he remained perfectly comfortable. After aspiration the splashings became much louder, but gradually disappeared, and were by August 9 replaced by a rub. This was at first heard over the whole of the cardiac area, but at the time of his transfer, on August 19, was limited to the apex and was not heard with every beat of the heart.

There was a fracture of the fourth rib near its junction with the sternum, and also of the seventh just behind the posterior axillary line.

The interest of this case lies in the mildness of the symptoms and the rapidity of recovery. The constant slowness of the pulse, which was always regular and of good volume, and not above 38 in spite of frequent doses of atropin, was remarkable.

Another feature of interest was the almost instantaneous effect of atropin on the oedema of the lungs and its consequent relief of the dyspnoea.

He was X-rayed just before he was transferred to England, and it was seen that the heart shadow was still enlarged slightly in both directions. The chest was otherwise perfectly clear, and both sides of the diaphragm were well defined and moved freely.

Case II. A case of perforation of the abdominal aorta, death not occurring until over three weeks after the wound.

Corporal R., aged 32, was admitted on May 6 with a history of having been wounded on May 1. He had suffered from a moderate amount of haemoptysis and had been dyspnoeic, but had complained of no abdominal symptoms. On examination the temperature was 101·6° and pulse 116. He was slightly dyspnoeic, but still complained of no abdominal symptoms. There were two nearly healed wounds (one in the left axilla and the other just behind the vertebral border of the left scapula) which were thought to be due to a bullet which had probably not penetrated the pleural cavity. The chest signs were slight and thought to indicate either a traumatic pneumonia or a small haemothorax. The X-rays showed slight opacity at the left base and obscuring of the left diaphragm. The chest was needled with a negative result. The abdomen was supple and not tender. There was slight jaundice of the conjunctivae. For a few days his condition improved. The temperature rose to 101–2° in the evenings, but the pulse averaged only 88.

On May 17 he began to vomit frequently and to complain of generalized abdominal pain. The abdomen was supple but distended, and there was generalized tenderness. Rectal examination was negative. The chest signs had disappeared, except for those of bronchitis in both lungs. He was treated with pituitary injections, enemata, and dextrose solution rectally, everything by mouth being withheld. These measures relieved the distension and vomiting, but the pain continued, and by May 20 became localized to the right side of the abdomen. There was now some resistance to palpation on the right side and especially in the right iliac fossa. Rectal examination was again negative. The temperature was still high (101°) and the pulse 100. A diagnosis of possible appendicitis was made and a laparotomy was performed. Beyond much generalized distension and some old appendicular adhesions no cause for the abdominal symptoms was discovered. There was no blood in the peritoneal cavity and no excess of fluid. The pain and vomiting continued, the temperature remained high, and the pulse became progressively weaker and more rapid, and the patient died on May 23.

At the post-mortem examination it was found that there was a resolving pneumonia at the left base. The tract of the shell fragment showed that it had penetrated the left pleural cavity and had perforated the diaphragm. The hole in the latter was plugged with omentum. There was a large septic retro-peritoneal haematoma, and it was seen that there were two minute perforations in the abdominal aorta. No intestinal lesions were present. The haematoma did not form a definite lump, but raised the whole of the posterior parietal peritoneum.

Case III. A case of perforation of the first part of the aorta, death not occurring until six days after the wound.

Corporal S. was admitted on August 31, 1916. The history was that he had been wounded on the right side of the chest on August 25. There was a small haemothorax on the right side, but the patient had been quite comfortable with a low temperature not above 100° and a good pulse averaging about 80.

On the morning of the 31st he collapsed suddenly at 9 a.m. and became pulseless. He remained in this condition all day. He had been given stimulants and morphia, but these had had no effect in restoring the pulse. On admission he was exceedingly pale, the temperature was subnormal, and the pulse was not palpable at the wrist; counted at the apex the rate was about 130.

The chest was resonant in front and the cardiac dullness was normal in extent. No apex beat could be felt. The breath-sounds in front were normal. Behind there was dullness up to the spine of the right scapula, with impaired breath and voice sounds. On the left side there was an impaired note and faint bronchial breathing up to the inferior angle of the scapula. Râles were present in front over the whole of the chest and at the left base, but not at the right base. A needle was put into the right side and blood found. A film from this was prepared, but no organisms were seen. In spite of the man being obviously *in extremis*, he was quite cheerful and his mental condition was clear. He was slightly but not very restless. It was thought that he was suffering either from a very acute infection or a secondary plural haemorrhage. The signs, however, did not suggest a large enough haemorrhage to account for the severity of the condition, and the absence of organisms in the fluid contra-indicated any operative procedures on the haemothorax.

Morphia, gr. $\frac{1}{4}$, was given, and a pint of saline was run into a vein and two pints were given subcutaneously. He only lived for a few hours after admission. It was noticed that for about half an hour before death he suffered from some spasm of the larynx.

At the post-mortem examination it was found that there was a moderate-sized haemothorax on the right side and a few ounces of blood in the left pleural cavity. The pericardium was enormously distended with blood. A small perforation was seen in the upper part of the pericardium and also in the first part of the aorta. The piece of metal was not found. The perforations were about 1 mm. in diameter.

The main interest of the case lies in the length of time that the man lived after the wound—six days. Presumably the perforation of the aorta was not complete at the time of the injury, but that ulceration into the lumen had occurred on the 31st and had caused the sudden collapse. The physical signs were unusual in that the only signs of a collection of fluid in the pericardium were those of compression of the left lower lobe. The bronchial breathing heard here was thought to be due either to a contra-lateral pneumonia or possibly to compression by the right-sided haemothorax. Probably the area of cardiac dullness was not increased because the bulk of the fluid lay behind and also because the dullness was masked by compensatory emphysema of the uncompressed part of the left lung.

Case IV. A case of haemothorax in which clotting interfered with efficient aspiration, treated by evacuating the clot and closing the wound completely.

Private B., aged 23, was admitted on July 21. He had been wounded in the chest two days previously. On admission there were entry and exit wounds caused by a piece of shrapnel which had penetrated the right chest from before backwards. There were signs of a large right-handed haemothorax. The apex beat was felt behind the left mid-axillary line. The patient was moderately distressed ; temperature 100·4°, pulse 124. He was aspirated on July 26, up to which time morphia was given freely. By aspiration only 20 oz. could be drawn off, although the canula could be moved about freely and it was obvious that it was in a large cavity. The fluid was reported sterile. The aspiration did not relieve his symptoms greatly, and the position of the apex beat remained unaltered. A second attempt was made the next day, but this time only about 5 oz. could be drawn off. On August 1 an attempt was made to draw off the clot by means of a large bladder trocar and cannula, the latter being connected with the aspirating bottle. This proved unsuccessful, only an ounce or two of fluid being obtained. The position of the apex beat and the signs remaining unaltered, it was decided to make a large opening into the chest and to evacuate the clot. The operation was performed by Capt. F. D. Saner on August 5, i. e. eighteen days after the wound. A flap was raised in the right axilla ; about three inches of the fifth and sixth ribs were cleared of periosteum ; the distal ends of the denuded portions were cut through and the proximal ends nearly so, and this enabled the portions of ribs to be bent back. The pleura was then incised. It was found that there was a large cavity full of blood-clot of a very spongy nature. The walls of the cavity were very thick, but that the lung was capable of, at any rate, some expansion was shown by the fact that the cavity was definitely smaller at the end of the operation. The clot was removed (digitally and with a blunt curette) as far as possible, and the cavity was then irrigated with saline. The pleura was sewn up, the ribs bent back into position, and the periosteum, muscles, and skin sutured separately. At the end of the operation the apex beat had come in slightly, but was still as far out as the anterior axillary line.

On August 8 (three days later) the apex beat was slightly farther out. Fifteen ounces of blood and some air were aspirated. The apex was then just outside the nipple. The next day it was in the anterior axillary line. From that time it gradually and persistently came in, and by the time when the patient was transferred to England was less than half an inch outside the nipple line. The signs suggesting fluid persisted on the right side of the chest, but a further needling was negative, showing that they were due merely to thickening of the pleura. The patient was allowed up on August 11, and was walking about in a day or so. The wound healed without suppuration.

The interest of the case lies in the fact that it is comparatively rare for clotting to interfere with efficient aspiration. If this happens, however, a much better result is to be expected if the clot is evacuated and the wound completely closed than is obtained by resection and drainage. There were no signs in this case of the clot softening and so becoming amenable to aspiration, and the man's general condition and the displacement of the heart rendered operative interference necessary.

Another point shown in this case was the early adhesion of the mediastinnm to the side to which it had been displaced.

Case V. A case of infected haemothorax with a pericardial effusion, treated by aspiration and not by resection.

Corporal M. This patient was admitted on September 8, 1916. He had been wounded about ten days previously. There was a shell wound with no exit wound. On examination he was found to be suffering from a small right-

sided haemothorax. There was a loud and extensive pericardial rub and signs of a definite pericardial effusion, which latter was verified by means of the X-rays. The patient was exceedingly pale, and the pulse, though only 92, was weak and of very poor volume. The temperature was 102°.

The haemothorax was aspirated on the day of admission, 15 oz. of altered blood being drawn off. This was found to be infected by streptococci. Since the general condition improved very satisfactorily and the signs did not suggest any filling up of the haemothorax, it was decided to watch the patient and not to resect at once. The pericardial signs gradually diminished, and by repeated X-ray examinations it was seen that the pericardial effusion disappeared completely.

Apart from the fact that the patient had an evening rise of temperature to 99–100° for nearly six weeks, his general condition left nothing to be desired, the pulse averaging about 80. His colour steadily improved, he put on weight, and his appetite and sleep were excellent, the latter without any form of opiate being necessary. He was allowed up for part of the day for several weeks before the temperature had quite settled, and this was found not to increase the pulse-rate unduly or to exhaust the patient. On October 12, since there were still signs at the extreme base of the right lung, he was again explored, this time 9 oz. being obtained. The fluid had no odour and in appearance was the same as the first specimen. There was no deposit of pus, and a microscopical examination of the film revealed no organisms. By culture, however, a growth of streptococci was obtained.

In view of the very satisfactory progress, in spite of the somewhat prolonged though low-grade pyrexia, there is little doubt that in this case the result was infinitely better than would have been obtained by resection. The likelihood that at this late date resection will have to be performed is small, but even should this have to be done, there will be a small cavity (containing at the most 10 oz.) to deal with, and which by this time will be well shut off from the general pleural cavity. The smallness of the cavity, in spite of the thickness of its walls, should ensure its rapid obliteration and the subsequent good expansion of the lung.

Case VI. Abdomino-thoracic shell wound Hernia of perforated stomach through the diaphragm; double complete pneumothorax.

This patient was wounded on May 6, 1917. He was admitted here on May 13, 1917. There was an entry wound low down in the left axilla and an exit wound in the right axilla. Before admission there had been haemoptysis, and the patient had vomited continuously, and had suffered from hiccough. At the casualty clearing station a diagnosis was made of left pneumothorax, small right-sided haemothorax, and possibly perforation of the oesophagus.

The pneumothorax on the left side had been aspirated, and blood had been found at the right base with the exploring needle.

On admission, seven days after the wound, the patient was very distressed, and vomited continually, but the hiccough had ceased. The vomit contained altered blood. The pneumothorax was again aspirated, and this gave great relief. Morphia was given freely and everything by mouth was withheld, glucose solution (6 per cent.) being given per rectum six-hourly. The vomiting ceased and the patient progressed well until the following day, when he collapsed somewhat suddenly. On examination he was then very cyanosed and dyspnoeic, and was nearly pulseless. There was a very bad air entry on both sides, and it was found that there was a double complete pneumothorax. A needle was inserted into each pleural cavity and oxygen was given. Relief was almost instantaneous. The needles were removed after some hours, but it was thought advisable to insert a small intercostal drainage-tube on the left side in order to prevent the recurrence of the symptoms. It was then found that swallowed fluid was discharged through this opening. The general condition of the patient,

however, improved steadily. With a view to determining whether any fluid was passing on to the intestines, a solution of methylene blue was given by mouth. This immediately appeared on the dressings, but there was no subsequent colouring of the urine or faeces. At no time was there any abdominal distension, pain, or rigidity.

A laparotomy was decided upon, with a view to performing a gastrostomy if necessary. The operation was performed on May 16, 1917, by Capt. F. D. Saner. It was found that the liver was dislocated to the left, and that there was a large rent in the left side of the diaphragm through which the whole of the stomach was herniated into the pleural cavity. The stomach was adherent to the pleura and pericardium, and was replaced in the abdominal cavity with difficulty. The laceration in the diaphragm was packed off with gauze. A perforation in the cardiac portion of the stomach was found and sutured. This hole appeared to be due to ulceration rather than to perforation by the shell fragment. The stomach and liver were sutured to the parietal peritoneum and the wound was closed. The patient stood the operation moderately well, but succumbed to shock some twelve hours later.

The sudden collapse and the acute right-sided pneumothorax were probably due to the suddenly increased pressure in the left pleural cavity owing to the perforation of the stomach.

It was remarkable that there were no abdominal signs associated with such a severe injury, and also that the man survived for ten days after the wound. The X-ray examination, made just before the laparotomy, showed that there was no damage to the pericardium and that the effusion in the right pleural cavity was very small.

This case was admitted after the rest of this paper was completed, but its interest seemed to justify its inclusion.

In conclusion I would wish to acknowledge my indebtedness to Millicent, Duchess of Sutherland, who has taken such a keen interest in the patients and who has been able to do so much for their comfort. I should like to thank my colleagues Capts. O. G. Morgan and F. D. Saner and Surgeon E. G. Schlesinger for their valuable help and suggestions in many of the cases, and Sister White of this hospital for her great assistance in the X-ray examinations of the paper. Good nursing is perhaps of more value in the after-treatment of infected haemothorax than in any other class of case, and on it depends to a very large extent whether good or bad progress is made, and I should like to express my appreciation of the skilful and sympathetic manner in which this part of the work has been carried out. Great assistance in the laboratory work has been afforded by Pte. J. Gowans, R.A.M.C.

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ON SULPHAEMOGLOBINAEMIA

By W. C. LONG and E. I. SPRIGGS

(From the Duff House Laboratories)

In vol. vii of this Journal Dr. R. L. Mackenzie Wallis gave a brief account of the cases of sulphaemoglobinaemia hitherto recorded. He also reviewed the literature of the disease, which was first described by van den Bergh, and communicated the results of his own researches. At that time there were eleven authentic examples. The condition has probably been recognized more than once since then, but is rare enough to justify a detailed description of another case.

An unmarried lady, aged 32, was admitted on September 14, 1916. The complexion was pale, the lips blue.

She stated that she was always 'breaking down', and complained of constipation, nausea, frequent vomiting, a constant ache below the right costal margin, pain in the lower part of the abdomen, also in the head, back, and limbs; and of weakness and fatigue.

Her parents were living and healthy. Two brothers were alive, one the subject of chronic phthisis.

The *medical history*, as related by the patient, was as follows: When a few months old she had an abscess in the brain, from which she nearly died. She does not think there were any fits or convulsions. Adenoids and tonsils were removed in early life. She had always been nervous and considered peculiar. At school she had attacks of vomiting and pain in the abdomen. These would last as long as a month. Such an attack was at least once brought on by a fright. In the intervals she was well and able to take ordinary food, but always constipated. At this time she was stout.

At 17 she had a sudden attack of severe pain in the left lower abdomen, and was in bed for a month. The left kidney was explored and drained, but no sufficient lesion found to explain the symptoms. A long period of ill health followed, spent in nursing homes, and she became thin. The attacks of vomiting ceased, but she suffered from a severe 'chill', causing fever and diarrhoea with blood in the stools. This was diagnosed as colitis and treated with intestinal douches.

From the age of 15 to 25 she was sometimes told that she looked intoxicated, and at these times, though there was no unconsciousness, or physical or mental discomfort, she lost grasp of what was happening for an hour or two or longer. There was no personal grief or worry to account for these feelings.

At 25 the appendix and a band of adhesions were removed. Later, repeated attacks of severe pain occurred in the right flank, frequently causing vomiting.

At 27 right laparotomy was performed and adhesions removed, after which no further pain was felt in that region; but she was often laid up in bed and in charge of nurses, suffering from frequent faintness, anaemia, sleeplessness, and persistent constipation, but without severe pain.

In July 1915 (aged 31) she had cystitis, since when there had been irritation of the bladder. In the latter part of the year she was helping in an infirmary, though in poor health, becoming easily fatigued and inclined to be hysterical. One night she suddenly felt faint, suffocated, and numb, and her colour became blue; she did not lose consciousness and knew what was going on around her. This was the first attack of cyanosis of which she is aware. The blueness persisted and soon after she had a similar sudden attack, which lasted for some hours and left her very weak. Constipation was still troublesome.

In July 1916 severe pain was felt below the right costal margin, passing through to the back. No fever, vomiting, or rigor occurred, though she frequently felt faint. This pain persisted, though less severely, until she came to Duff House.

Menstruation began at 14 years of age and was usually irregular. A year ago a severe haemorrhage occurred and caused faintness. For the past six months there had been amenorrhoea. For some months she had occasionally a brown offensive vaginal discharge. This was not complained of during her stay.

Symptoms on admission. Constipation. She had always taken aperients since childhood. A motion was usually preceded by colicky pain.

Vomiting. Frequent, and commonly without nausea. The act of stooping down after an ordinary meal, sudden excitement, or fright, or certain foods, especially cream and milk, might bring it on.

The *appetite* was capricious.

Pain. A constant ache below the right costal margin, sometimes sharp, severe, and extending through to the back. It had no particular relation to food or occupation, was accompanied by nausea and sometimes by sickness. There was also general discomfort in other parts of the abdomen, 'a gnawing, aching sensation,' especially in the hypogastrium. A severe ache was frequently complained of in the sacral region, usually worse at night and increased at the periods. Other pains were complained of in various parts of the body and limbs, and neuralgic pains in the right side of the head and neck, particularly affecting the right ear: these were sometimes relieved by aspirin.

Palpitation would occur without excitement or exertion.

The patient *felt tired* and 'not sure of herself'.

Examination. The complexion was pale, dull, muddy, and dark round the eyes, which were a little prominent. The lips were bluish, the features tired and expressionless. The skin was dry, though there was sometimes profuse perspiration at night. The forearms showed slight subcutaneous swelling which did not pit on pressure. There were mild bruises on the arms and legs: the patient said that she bruised easily. The manner was composed and agreeable, though cerebration was rather slow: she was vague in giving an account of herself, but spoke of pain and discomfort in superlatives. The temperature was normal.

The tongue was clean. The teeth were partly artificial, deficient in molars, and carious; the gums were pale and firm. The pharynx was pale, dry, and cicatrized. The thyroid was natural. No enlarged glands were felt. The abdomen was flat and its walls thin. On the least pretence of an examination being made the muscles were rigidly contracted, making satisfactory palpation impossible. Considerable pressure revealed tenderness below the right costal margin. The area of splenic dullness was enlarged, extending from the sixth rib to the costal margin. The spleen could not be felt.

The cardiac impulse was in the fourth intercostal space. A faint systolic

bruit accompanied the first sound at the mitral area. The pulse was regular, of poor volume; the blood pressure 135 mm. Hg.

The blood contained 65 per cent. haemoglobin, 2,350,000 red cells, and 5,400 white cells in the cubic millimetre. No abnormal types of cells were found. A differential blood-count of 500 cells gave:

Polymorphonuclears	58·4 per cent.
Small mononuclears	29·6 „ „
Large mononuclears	9·6 „ „
Basophils	1·4 „ „
Eosinophils	1 „ „

Blood cultures were sterile.

The knee-jerks were absent, but other nervous reflexes were normal.

An X-ray examination after a barium meal showed that the stomach was long, contracted to a tubular shape, and emptied rapidly. The bulk of the meal left the stomach in twenty minutes, though there was a small residue for four hours. There was delay at one point in the jejunal coils. Ileal stasis was present, material being still contained in the terminal ileum six hours after the stomach was empty. There was great delay throughout the colon, especially in the proximal portion, the bulk of the meal lying in the transverse colon and only a small portion having reached the pelvic colon at seventy-two hours.

A twenty-four hours' collection of urine, taken on admission, measured 920 c.c. and contained diacetic acid and acetone.

The stools were reddish-brown, partially fluid, offensive, and contained much undigested vegetable matter and varying amounts of mucus.

A *provisional diagnosis* was made of severe anaemia with cyanosis of unknown cause.

Progress. On the third day after admission the patient began to vomit all food taken. The vomiting was seldom preceded by nausea or other discomfort. Solid and liquid food as well as medicine were brought up without effort a few minutes after being swallowed. The vomiting continued for about two weeks. Nutrition suffered very little and the general physical condition remained unaltered. During this period the urine was diminished to 200 to 400 c.c. in twenty-four hours, the total nitrogen varying from 1·7 grm. to 3·6 grm. Diacetic acid and acetone disappeared from the urine the seventh day after admission and did not reappear.

Pain and discomfort in the bladder were frequently complained of and could not be explained. The quantity of urine became further diminished, the total collection in twenty-four hours varying during October from hardly any to 250 c.c., the average being 107 c.c. As at this time the total nitrogen was only 0·7 to 2·0 grm. per diem, whilst that in the food retained was about 5 grm. per day, and diacetic acid and acetone were absent, we could not avoid the suspicion that all the urine did not reach the laboratory; but though precautions were taken, this was not proved.

The abdominal pains varied in site and character, the most constant and severe being below the right costal margin. The patient lay on her back or side with the right thigh flexed on the abdomen and the knee drawn up to the chest. If questioned, she would say the pain was very severe, but otherwise did not complain or appear to be in great distress. The temperature and pulse were normal; no rigors or sweats occurred. Various measures to relieve this pain were tried unsuccessfully. Morphia was given hypodermically on three or four occasions, but seemed to excite without giving relief. Insomnia was persistent.

Early in October, while lying on a couch in the open air, the patient became dusky in colour, looked very vacant and strange, and appeared to have fainted. The nurse who was summoned and had her removed to bed was alarmed and thought she had had a 'heart attack'. She quickly became more blue, and was

unconscious for a short time. When seen later she was conscious but exhausted, and could give no account of her attack. Cyanosis was obvious, and, though gradually lessening, it did not entirely disappear before the second attack, which occurred a few days later.

Second attack, October 16. The patient had felt poorly all day, but had been unusually free from pain. She took no meal in the evening, but was sitting up and talking to friends in her room. At 8 p.m. she looked strange, had a vacant stare, appeared to be fainting or going into a swoon, and then rapidly became unconscious. At 8.45 p.m.—that is, three-quarters of an hour after the onset—she was lying flat on her back in bed. Her appearance gave the impression of a dying person. The skin was of a dusky leaden colour, an extreme pallor, modified by the bluish tint. The lips, nostrils, and mucous membrane of the mouth were a dull deep purple. The extremities were a lavender-blue colour, best seen in the nails. She was apparently unconscious. The eyelids were half open and the eyes staring fixedly to the right. The corneal reflex was slow and feeble. The pupils were dilated, but reacted to a bright light stimulus. The body and limbs were warm, partly due to the hot bottles and blankets provided. The limbs were flaccid, and there was no rigidity of any of the muscles. The abdomen could easily be palpated and the opportunity, not previously afforded, was taken to examine it carefully. Nothing abnormal could be felt.

The temperature was 97° F. in the axilla. The pulse was 90, regular, a little smaller than usual, but of fair volume. The heart sounds were regular. A soft systolic bruit accompanied the first sound, and could be detected all over the cardiac area, but was best heard at the apex. No bruit was heard in the vessels of the neck. Respiration was shallow, 18 to the minute. A deep sighing inspiration occurred at intervals of about forty-five seconds. There was no peculiarity in the odour of the breath. In the course of two hours she slowly became semi-conscious. The tongue moved to moisten the lips and the eyes were slowly moved from side to side. A teaspoonful of brandy was rejected, but sips of water were swallowed. Two pints of saline solution were given per rectum and retained for an hour and a half.

At 11.45 p.m. the pulse was 102, regular, and of fair volume. A draught containing liq. strych. ♏ 3, tr. digit. ♏ 5, and aq. camph. ʒ 1 was given and retained. The condition remained the same, but she could be roused, and moved her head in response to inquiries. She seemed to have pain, probably in the abdomen. At 1.20 a.m. the pulse was 88, and improved in character. Respiration was more natural. She was then conscious and able to speak, complained of numbness all over the body, but had no pain. The strychnine draught was continued two-hourly.

In the morning she had more or less regained her usual appearance, though cyanosis was still deep and she was a good deal exhausted. During the next few days the blueness gradually lessened, but did not disappear.

A third attack took place on October 22, lasting for a little over three hours, during most of which she appeared to be unconscious. The patient had two other attacks during her stay, in all five in seven weeks. Unconsciousness appeared to be complete so far as pricking with a pin and other signs indicated.

Annoyance or disappointment was liable to be followed by an attack.

As there were no cardiac or respiratory symptoms to explain the attacks, nor any signs of thoracic disease, a diagnosis of enterogenous cyanosis as described by Dr. Garrod in Allbutt and Rolleston's *System of Medicine* was made. The term includes cases of methaemoglobinaemia, due usually, though not always, to drugs, and sulphaemoglobinaemia, so far of undetermined causation. The blood was then examined with the spectroscope and found to contain sulphaemoglobin.

Spectroscopic Examination of the Blood.

The blood drawn for examination was always dark and frequently of a deep chocolate colour. On November 2, blood was taken, defibrinated, and examined in various dilutions, the most satisfactory being 1 in 20 and 1 in 30. Similar dilutions of normal blood were used for control. An absorption band was seen to the left of D in the red. It coincided with the band of artificially prepared sulphaemoglobin when compared by means of a superimposed spectrum. When compared with the spectrum of artificial methaemoglobin, the band of the patient's blood was nearer to the right or violet end. The addition of ammonium sulphide solution caused no alteration in the appearance of the band in the patient's blood, whilst that of methaemoglobin disappeared. Acid-free carbon monoxide, passed through the patient's blood, caused the band to move to the right. The measurements of the band are shown in the accompanying table, with the corresponding measurements given by Wood Clarke and Mackenzie Wallis, as quoted by the latter.

	Patient's blood.	Wood Clarke.	Mackenzie Wallis.
Band of sulphaemoglobin .	615–31	613–29	613–25
On addition of CO . .	609–28	605–20	
Artificial methaemoglobin .	621–44	620–45	

At a second examination (December 10), when cyanosis was less pronounced, the sulphaemoglobin band was again distinct, but on dilution it disappeared sooner than on the previous occasion. The band could be seen in the lobe of the ear with an ordinary electric lamp and a pocket spectroscope.

By this time (November) the general health had suffered a good deal, and the patient was thinner and weaker. More or less cyanosis was usually present. Nourishment was taken with difficulty and vomiting occurred occasionally. Discomfort in the abdomen was constant and sometimes severe pain was complained of and lack of sleep.

Early in November another X-ray examination was made after a barium meal. The stomach was constricted and presented an hour-glass appearance. The constriction rapidly relaxed on pressure, but with a strong tendency to contract again. The stomach emptied in eight hours. The jejunal delay previously seen was less noticeable, but some coils appeared to be bunched and partly fixed in the right subcostal area, corresponding to the site of pain usually felt. There was still moderate ileal stasis, and general delay in the colon, with irregular segmentation in the latter.

The temperature was normal throughout with the exception of a slight rise for forty-eight hours, for which no cause was discovered.

The vomits usually consisted of freshly ingested food and frequently contained no free hydrochloric acid.

On October 22 a blood examination showed Hb. 60, red cells 3,200,000, white cells 7,400; the Hb. being slightly less and the red cells rather more than on admission.

Further Observations on Blood, Urine, and Saliva.

In the earlier cases nitrites were found in the urine. The observation must be made on fresh acid urine, for van den Bergh and Gutterink showed that any urine which has begun to ferment, or any fluid which has stood in air, may contain nitrites. As nitrites can form methaemoglobin from oxyhaemoglobin, and urine, with or without nitrites, can slowly effect the same change, attention has been paid to the urine and to nitrites in sulphaemoglobinaemia also.

In the cases observed by Dr. Mackenzie Wallis, nitrites were found frequently in the urine and in the saliva. Their presence in the saliva did not correspond to the variations of cyanosis, but the test was more often negative as the patient's condition began to improve. A bacillus which produced nitrites was grown from the saliva. He found the blood-serum also contained nitrites. Van den Bergh and Gutterink, after taking precautions to exclude nitrites in the air, did not find them in the serum, but found them in the corpuscles. They suggested that the nitrites might be formed by a specific micro-organism.

Dr. Wallis also found that the serum of these patients possessed the power of rapidly reducing oxyhaemoglobin. Observations were, therefore, made on these points.

The Serum.

Serum from the first specimen of blood withdrawn (November 2) gave a positive reaction to the metaphenylene-diamine test for nitrites. On the second occasion, when cyanosis was less definite, the serum did not show the presence of nitrites with the Griess-Ilosvay reagent (naphthylamine test).

In order to see if the serum of the patient's blood would reduce the oxyhaemoglobin of normal blood, a flat glass cell was made of such a thickness as to show the two oxyhaemoglobin bands separately in a dilution of 1 in 20 of defibrinated normal blood. 0·5 c.c. of the diluted normal blood was put in the cell and 0·1 c.c. of the patient's serum (December 10) added and mixed gently. There was no change in the spectrum in half an hour at room temperature. Increasing additions of the patient's serum were then made to 0·5 c.c. of dilute normal blood, up to equal quantities of each, both at room temperature and at 40° C., but no alteration of the spectrum resulted beyond the effect of the dilution. It is to be noted that cyanosis was not severe at this time; though the sulphaemoglobin band was present in the diluted blood, and could be seen through the lobe of the ear.

The Urine.

Daily analyses were made. Diacetic acid and acetone were present during the first week of admission, but later were usually absent. Albumin, sugar, blood, and indican were not found. The small amount of urine and of total nitrogen has been mentioned.

The proportion of ethereal to total sulphates was found on five occasions to be very variable: 1 : 5, 1 : 47, 1 : 22, 1 : 10, 1 : 3. The second and fourth of these observations were made at the time of an attack.

During the attack of November 8 no nitrites were found in the urine; during that of November 30 a trace was present, and a faint trace on December 4; on the 6th, 7th, and 8th none was found. On the last date there was a strong nitrite reaction in the saliva.

Bacteriological Examination of Saliva.

By Dr. Duncan, Lecturer on Bacteriology at the University of Aberdeen. The saliva gave a faint nitrite reaction. A similar reaction occurred in a small proportion of samples from normal individuals. The saliva was inoculated into nitrite-free gelatine, broth, and milk. The culture tubes were divided into two groups, one group being incubated under aerobic conditions, the second under anaerobic conditions. In each group tubes of every medium were incubated at room temperature, at 22° C., and at 37° C. Nearly all the tubes under all

conditions gave a fairly copious mixed growth of bacteria, with a certain amount of gas-production in some cases. Tests were made at intervals up to a fortnight for the presence of nitrites, the Griess-Ilosvay reagent being employed in all cases. None of the tubes gave any nitrite reaction. Similar results were obtained with a second collection of saliva. The incubation of the saliva itself at 22° C. and 37° C. was also tried, but no nitrite reaction was obtained. Lastly, no nitroso-bacillus was found in the cultivations.

Remarks on the Foregoing Tests.

The observations made were to a large extent inspired by the interesting work of Dr. Mackenzie Wallis. It has long been known that sulphaemoglobin is formed when H_2S is passed through blood. But as H_2S is often present in the bowel, some explanation is needed as to why sulphaemoglobinaemia is rare. Van den Bergh thought that the slow constant development of H_2S in a condition of great intestinal delay was the cause of abnormal absorption. His view received support from the observations that his first patient, who suffered from a rectal constriction, recovered when the constriction was removed, and that his three other patients were all better so long as a daily action of the bowels was secured. Delay in the bowel, however, or even obstruction, is also much commoner than sulphaemoglobinaemia, suggesting the necessity of some additional factor.

Wood Clarke and Hurtley having shown that sulphaemoglobin can be formed from oxyhaemoglobin by strong reducing agents in the presence of the merest traces of sulphuretted hydrogen, Dr. Wallis, following up their work, suggested that a nitroso-bacillus, which he found in the saliva, formed, in addition to nitrites, a strong reducing substance which is easily absorbed into the blood-stream, a trace of sulphuretted hydrogen being presumably derived from the intestinal tract. He found the nitrite-producing bacillus in the saliva of the five cases he examined. When growth of this bacillus occurred with utilization of amino acid a strong reducing substance appeared in addition to the nitrites. Further, in three cases in which it was tried, an addition of the patient's serum to a dilute solution of normal blood led to the replacement of the oxyhaemoglobin bands by the band of reduced haemoglobin, with a corresponding change of colour of the solution, indicating the presence in the serum of these patients of a reducing substance more potent than could be explained by the presence of nitrites.

Dr. Wallis concludes that it is 'highly probable that this nitroso-bacillus had some definite relation to sulphaemoglobinaemia, but until more cases have been investigated no definite pronouncement can be made'.

The idea that the blood of the patient contains a reducing substance, the presence of which in increased quantity causes the attacks of severe cyanosis, is an attractive one, and would also explain the good effect of the inhalation of oxygen. It may be remarked, however, that the observations hitherto recorded do not show that the reducing substance produced by the growth of the bacillus

in vitro is the same as that found in the patient's serum. It would be of interest also to know whether the strong reducing power described is possessed by the plasma; and whether the serum or the plasma can reduce a solution of the patient's own blood; or if it must be assumed that the patient is in part immune from its full activity, as extensive reduction of oxyhaemoglobin to reduced haemoglobin in the arteries as well as in the capillaries would presumably be incompatible with life unless the lungs reoxygenated the blood; whereas this complaint is not a fatal one, and in our patient, even when cyanosis was severe, there was no dyspnoea. The circulating blood as seen in the lobe of the ear appeared natural as regards the oxyhaemoglobin bands. If a reducing agent of such strength were present during life, it would have to be supposed that whilst it was active in aiding traces of H_2S to form sulphaemoglobin, it was prevented from reducing oxyhaemoglobin to any great extent.

In this case Dr. Duncan failed to obtain a nitroso-bacillus from the saliva on two occasions, the technique followed being similar to that described by Dr. Wallis. Further, the serum of this patient was not found to have the power of reducing the oxyhaemoglobin of a solution of normal blood. The sulphaemoglobin band was present in the blood when this test was made, but the cyanosis was milder than it had been. The reducing power of the serum from blood drawn during an attack of severe cyanosis with unconsciousness was not tested.

Treatment.

During the attacks of vomiting all food was either refused or vomited, and saline rectal infusions were given. Gastric and intestinal sedatives, such as bismuth, belladonna, morphia, and chloretone, had little effect either on the sickness or pain. For sleeplessness, bromides, chloral, veronal, and Dial (Ciba) were used frequently.

Before the condition was recognized as one of sulphaemoglobinaemia, a purely milk diet, which van den Bergh found successful in cases of methaemoglobinaemia with diarrhoea, was tried for a few days with no benefit; it was much disliked by the patient.

Later, a mainly carbohydrate diet, as recommended by the experience of others, consisting of such foods as bread, semolina, macaroni, boiled rice, starchy breakfast foods, plain cake, and biscuits, was taken. At the same time treatment was directed to clearing and cleansing the bowel by purges, douches, and intestinal antiseptics. Sulphate of magnesia in repeated doses and sodium sulphate were used. The bowel was also washed out daily with warm saline solution. Permanganate of potash in 1-grain pills, izal in 2-minim capsules, and beta-naphthol in 5-grain cachets were tried in turn. Such measures appeared to cause some improvement, both of the cyanosis and the abdominal discomfort. The diet was, however, irksome, and towards the end of November eggs, chicken, milk, vegetables, and fruit were given. These additions were followed by an aggravation of symptoms; vomiting recurred, abdominal pain increased, and cyanosis returned. A return to the former diet was again followed by improvement. During the last attack of unconsciousness, in November, oxygen was given and appeared to lessen the cyanosis and shorten the attack.

Later History.

After the patient returned to her home the carious teeth were removed. Dr. C. C. Cuthbert has kindly informed us that she is much better and has put on some weight. 'She still has her turns of cyanosis, but they are not so severe, and not nearly so frequent. Very often six weeks or two months will elapse between them.'

Remarks on the Clinical Features.

The twelve cases known to us are those of van den Bergh, 1; van den Bergh and Gutterink, 3; West and Wood Clarke, 1; A. E. Russell, 1; Essex Wynter, 1; Wood Clarke and Curts, 1; Haldin Davis, 1; Mackenzie Wallis, 2; and the present case. Dr. Wallis's paper also included a re-examination of the case previously described by Haldin Davis.

Cyanosis was, of course, present in the twelve cases. Constipation was present in ten of them, and probably in eleven. It is remarkable that the only two cases which are reported as recovered are van den Bergh's case, in which constipation was cured by an operation on a rectal stricture, and Dr. Wallis's case, under the care of Dr. Garrod, in which the bowels were not constipated as a rule. A detailed account of symptoms in van den Bergh's second, third, and fourth cases is not given, but taking the others, the symptoms complained of, in order of frequency, were: weakness, in six cases; headache, in five; fainting or unconsciousness, sleeplessness, in four; vomiting, anaemia, dyspnoea, bruising, dental caries, scanty urine, neurosis, pyrexia, in two cases each.

The characteristic features of the complaint are the cyanosis, constipation, debility, and headache. These were all prominent in our case. In addition there were nausea, frequent attacks of vomiting, pains in various parts of the body, numbness or a feeling of paralysis, sleeplessness, faintness, palpitation, scanty urine, and neurotic or hysterical manifestations. Two operations have been performed on account of the abdominal symptoms, but no sufficient cause for the complaint has been found, and it is possible that the constant and sometimes spasmodic abdominal pain could be accounted for by adhesions and more or less arrest of the intestinal contents, such as was found by X-ray examination. The vomiting was, we think, partly a neurosis. It is difficult to state the duration of the illness. The patient had never been healthy, always constipated, for many years suffered abdominal symptoms suggesting delay in the bowel, and had been diagnosed as a case of intestinal toxaemia. Attacks of cyanosis, associated with a semi-comatose condition, first occurred a year before admission, and this time may be taken as indicating the onset of sulphaemoglobinaemia.

Observations on the saliva as described by Dr. Mackenzie Wallis did not in this case yield the results he obtained as to the presence of a nitroso-bacillus. It is possible that the good results which followed the use of a vaccine in one of his cases were due to the removal of carious teeth. Benefit appeared to follow the extraction of bad teeth in this patient. It must be remarked, however, that

one patient (Dr. Ringrose's) in whose saliva Dr. Wallis found a nitroso-bacillus had no natural teeth.

The present case tends to confirm the view heretofore taken, namely, that the cause of the condition is to be sought in the alimentary canal, and that continued purgation offers at present the best means of treatment.

Summary.

1. A case of sulphaemoglobinaemia is described showing the usual features of cyanosis—constipation, debility, and headaches. The band of sulphaemoglobin was demonstrated in the blood and could be seen through the lobe of the ear.

2. The patient complained of much abdominal pain, for which two operations had been performed without any sufficient cause for the pain having been found.

3. There was a large element of neurosis.

4. Improvement followed a diet consisting mainly of carbohydrate foods, the use of purges and antiseptic medicines, and the removal of carious teeth; but the patient is still the subject of the complaint.

5. Attempts to confirm the findings, described in some other cases, of a nitrite-producing bacillus in the saliva and of a substance in the blood-serum which strongly reduces oxyhaemoglobin solutions were unsuccessful in this patient.

For the chemical examinations and much of the spectroscopic work we are indebted to our colleague Mr. A. B. Weir, B.Sc. Professor Niven, of Aberdeen University, kindly placed a large spectroscope at our disposal for measuring the wave-lengths of the absorption bands. The bacteriological examinations were conducted by Dr. George Duncan, of Marischal College, Aberdeen. We have made free use of clinical notes by Dr. D. Pickering. To these gentlemen we wish to express thanks.

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CLINICAL AND PATHOLOGICAL NOTES ON TRENCH NEPHRITIS

By W. H. TYTLER and J. A. RYLE

With Plates 1–4

THE condition known as 'trench nephritis' or 'war nephritis' has been the subject of so much investigation, and of so many contributions to the medical literature, that the mere routine clinical and pathological examination of a series of cases, carried out under the conditions of work at a Casualty Clearing Station, cannot be expected to add much that is new to the knowledge of the disease. The present paper makes no pretensions to a solution of the main problems of the subject, but has the object only of presenting the clinical features in a considerable number of cases observed during the early stages, and of putting on record the results of pathological examination in a series of cases which terminated fatally within the first three weeks of the disease.

The clinical notes are based on a series of 150 cases, all of which were under the direct care of one of us (J. A. R.). They represent the cases of this type of nephritis admitted to one Casualty Clearing Station during the early months of 1916 and the entire winter of 1916–17. They were all cases presenting constitutional symptoms as well as albuminuria, no cases being included of the prevalent albuminuria without indisposition, and none of the so-called 'lower tract' cases.

The fatal cases on which the autopsies reported were performed were collected from several Casualty Clearing Stations and field ambulances. For the opportunity of examining them we are indebted to the medical officers who had charge of them. Their names are too numerous to permit of individual acknowledgement.

We have adhered throughout the paper to the term 'trench nephritis' as being the one in most common use, although it is not completely accurate, since the condition is by no means confined to trench troops.

Clinical Notes.

Etiological factors. All the patients were necessarily males of military age, and within these limits were about equally distributed. All were employed in the forward area and the great majority actually in the trenches. There was commonly no history of any predisposing illness, nor were there any concurrent

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epidemics, such as scarlet fever or tonsillitis, which could be considered to bear on the etiology of the disease.

The seasonal incidence showed a marked increase during the winter months. As noted above, the cases described in this paper were observed during the early part of 1916 and the entire following winter. During the summer months of 1916 the cases were so occasional that consistent records of them were not kept. The following chart shows the admission rate during the winter of 1916–17:

Monthly Admissions of Trench Nephritis to No. — Casualty Clearing Station from October 1, 1916, *to March* 31, 1917.

October . . . 8	December . . 30	February . . 22
November . . 23	January . . . 18	March . . . 12

During the winter of 1916–17 the cases were derived from five divisions, each of which occupied the same position throughout these months. One division yielded 40 per cent. of the cases, the next highest 20 per cent., while the remaining three gave approximately equal numbers. There was nothing to indicate whether the high incidence in one division was due to geographical or to epidemic factors.

Clinical features. Onset. The history was usually of an onset from two or three days to two weeks previous to admission. The almost constant complaint was of shortness of breath on exertion, while swelling of the extremities and face was also very frequently noted. A history of cough and of a general feeling of unfitness was common. The history of onset did not suggest an acute febrile or septicaemic attack.

Clinical picture. On admission, and indeed throughout the early course of the disease, the most striking characters were pallor, oedema, and dyspnoea. Of the more severe cases, comprising between 20 and 25 per cent. of the whole number observed, the following is a general presentation:

The patients were pale and puffy, with oedema of the eyelids, face, feet and hands, and, after a short time in bed, of the back and flanks, which might show deep creases due to the pressure of folds in the bed-clothes. The abdomen, on palpation, was full and tense. The spleen, though often enlarged post mortem, was never palpable during life. The respirations were short and rapid, and the dyspnoea increased on the slightest exertion. There was impaired resonance and air entry at the bases, with or without moist sounds. The worst cases showed cyanosis of the lips and ears. Nearly all required a bed-rest to give them relief, while continuous administration of oxygen was sometimes necessary. Except as a terminal event expectoration was not commonly profuse. One case had a large bilateral pleural effusion, but in the remainder of the series pleural effusion was uncommon, and when present not of large amount, as borne out also by the autopsy findings.

During the months of December 1916 and January and February 1917, bronchitis was an almost constant complication. At this season it was extremely

prevalent among all troops in the region, as were also laryngitis and tracheitis, and there was also a small epidemic of acute purulent bronchitis, due in part to the influenza bacillus, and showing a relatively high mortality. The bronchitis, as a complication of the nephritis, was usually present on admission, and was undoubtedly a prominent cause of the severe respiratory symptoms. Also, in the fatal cases, it would seem to have been an important determining factor.

The dyspnoea was in our cases frequently urgent and distressingly obvious. So predominant were the respiratory signs that, until the condition became more generally recognized in the field ambulances, cases were not uncommonly sent down with a diagnosis of acute bronchitis or of pneumonia. From clinical evidence we consider the dyspnoea to be primarily due to pulmonary oedema, and this view was substantiated by the autopsy findings. Bronchitis was undoubtedly a great contributory factor, and swelling of the abdomen and of the tissues of the abdominal wall probably played a part.

We have frequently remarked a striking resemblance between the respiratory symptoms in trench nephritis and those seen in cases of gas-poisoning, particularly those due to phosgene.

The pulse, in nearly all cases, was full and bounding, and the blood-pressure was generally above 140 mm. of mercury. One case showed subconjunctival haemorrhages.

Pyrexia was not the rule save in relation to the bronchitis. A small group of cases, however, without apparent bronchitis, showed temperatures ranging from 100° to 104° F. during the first week of the disease.

Another small group of cases showed the respiratory picture described above, with the addition of prolonged expiration and the general symptoms of severe asthma, but with complete absence of external oedema. The presence of albumin and casts in the urine, and the relatively small amount of expectoration, served to distinguish this group from the cases of simple capillary bronchitis which were so numerous during the winter.

In spite of the anasarca and the pulmonary oedema the patients usually passed a quantity of urine not much below the normal amount. The figure in most cases was between 30 and 50 ounces. None of the cases with respiratory symptoms and oedema showed evidence of uraemia, and, indeed, there was only one case of this latter type in our series. This case showed no respiratory distress, and there was a marked diminution of urine. Our experience does not represent the true proportion of respiratory to uraemic cases, since during the same period other clearing stations had a relatively much greater number of cases with cerebral symptoms. Also we examined at autopsy several cases of sudden death with little or no previous illness which, we concluded, belonged to the class of trench nephritis.

Mortality and prognosis. In the fatal cases death usually occurred during the second week, as closely as could be determined. In such cases the terminal picture showed increased cyanosis, and very severe dyspnoea with profuse frothy

expectoration. Death in all the fatal cases in our series was apparently due to respiratory failure.

The mortality among cases of nephritis admitted to this Casualty Clearing Station during the winter of 1916–17 was 4 per cent. All of these fatal cases were of the respiratory type, and in all but one there was associated bronchitis. The immediate prognosis, then, in the absence of this very common complication, may be said to be good in the dyspnoeic form of the disease. The uraemic type, from the experience of those who have seen more of it, shows a higher mortality rate.

Treatment. As always, the first essential in successful treatment is early diagnosis. Cases which had been first recognized late in the disease were in general slower in their reaction to treatment. We would suggest that during the periods of high incidence of the condition an increased watchfulness for incipient pallor and dyspnoea would lead to better results in treatment.

Warmth and rest in bed with good nursing and the administration of saline purgatives, produced a rapid change in the condition of all cases of moderate severity. Postural treatment for the dyspnoea, and oxygen when necessary—given preferably by the continuous intranasal method—gave much relief. Hot packs were often beneficial, but seemed to be definitely contra-indicated in cases with pyrexia or severe bronchitis. The diet was customarily fluid, sometimes with the addition of light farinaceous foods. As far as possible patients were not evacuated until the symptoms had largely disappeared.

In uraemic cases bleeding and lumbar puncture may give relief, particularly the former.

Clinical Pathology.

The amount of investigation which has been done in this field is now so extensive that it is with hesitation we present the meagre figures at our disposal. Since, however, nearly all of this work has been done at a later stage of the disease, we give our results for what they are worth as bearing on the early stage.

Urine. The urine nearly always showed a large amount of albumin on admission, the amount being roughly proportional to the severity of the symptoms. In some cases there followed a very rapid diminution in the amount of albumin.

A small series investigated during the winter of 1915–16 by Captain Adrian Stokes, R.A.M.C., gave the following results:

Specific gravity varied between 1,012 and 1,018, with an average of 1,015.

Albumin varied from 0·1 to 2·5 per cent., with an average of 0·96 per cent.

Urea varied from 0·05 to 3·3 per cent., with an average of 2·06 per cent.

Of the entire series of cases only about 2 per cent. showed macroscopic haematuria.

Microscopically the centrifugalized urine showed numerous tube-casts, red blood-cells, and leucocytes. The number of casts, however, was usually smaller than in severe acute nephritis as seen in civil life.

Blood. Urea in the blood varied from 0·05 to 0·15 per cent., with an average

of 0·08 per cent. The amount did not seem to bear any constant relation to the amount of urea in the urine. (Captain Stokes.)

Leucocytes in a small series of cases were not definitely increased, the usual figure being between 8,000 and 10,000. Higher counts were not observed save with severe bronchitis.

The coagulation rate was investigated in a few cases, using Wright's method. We were not able to demonstrate a definite departure from the normal.

Gross Morbid Anatomy.

The description which follows of the morbid anatomy in trench nephritis is based on a series of twenty-five autopsies. In eighteen of these the diagnosis had been made during life and the patients had been under treatment in a Casualty Clearing Station. The remaining seven were cases in which the diagnosis had not been made clinically. They were men either found dead in their billets with no history of illness, or dying under unexplained circumstances within a short time of their first symptoms. The autopsies on these seven cases were performed by Captain Adrian Stokes.

The gross morbid anatomy in this series of twenty-five cases presented a picture which was by no means constantly clear-cut, but which in many cases was definite enough to make the diagnosis almost certain without clinical history or urine examination, and in all cases was suggestive enough to render it probable. The most constant gross changes observed were those seen in the lungs and spleen, consisting, briefly, in an extensive pulmonary oedema, often of rather characteristic nature and usually accompanied by a purulent bronchitis, and in the presence of characteristic haemorrhages throughout the spleen. A more detailed description follows.

External examination yielded little of significance save for the presence of anasarca in varying degree. This could usually be distinguished, though it was seldom as evident as during life. Pitting on pressure was rarely obtained to more than a slight degree post mortem, but on section the subcutaneous tissues were usually distinctly wet, as were also the areolar tissues surrounding the body cavities and viscera. The pleural, pericardial, and peritoneal cavities only infrequently showed serous effusion. Pleural effusion occurred in three cases, pericardial effusion—of small amount—in two cases, and ascites in two cases.

Lungs. The lungs constantly showed oedema, and usually of extreme degree. In most cases, and in our opinion characteristically, the lungs were extremely distended, with a smooth, moist, shining surface, pale grey or mottled, or sometimes congested at the bases, heavy, only slightly crepitant, and when cut pouring out a large quantity of pale frothy fluid. The lung tissue, however, was usually firmer and more elastic than in oedema due to mechanical causes, and the cut surface often had a somewhat gelatinous consistence, as though the air-cells were filled with a soft coagulum. This condition was

strikingly like that seen in cases of early death in gas-poisoning. The oedema was usually general throughout the lungs, but in three cases was definitely more evident in the upper lobes. There was not a constant relation between the extent of the oedema and the severity of the dyspnoea, but most of the cases with extreme respiratory distress showed at autopsy very pronounced pulmonary oedema. Diffuse congestion was not common, though many cases showed engorgement at the bases.

Evidence of bronchitis or bronchopneumonia was seen in most cases, more frequent and more severe during the months when such conditions were generally prevalent. Thus a certain amount of yellowish pus or muco-pus could usually be squeezed from the bronchioles, and in six cases indefinite nodules or patches of diffuse consolidation were found at the bases or apices. Emphysema usually occurred in the less oedematous portions of the lung, or diffusely where there was severe involvement of the bronchioles.

Spleen. The spleen was usually somewhat enlarged, though seldom as much as twice the natural size. On section it was fairly firm and not pulpy, but was usually congested and often yielded a large amount of fluid blood from the cut surface. The cut surface presented almost constantly an appearance which we have come to regard as highly characteristic of the disease. This appearance was caused by the presence throughout the spleen tissue of innumerable small haemorrhages. These had a serpiginous and often rather indefinite outline, and were seldom more than 2 mm. broad, although they might be irregularly linear and then reach a length of 5 to 7 mm. In many cases the haemorrhages were so evident as to strike the eye at once, but in others they might easily have been missed had they not been particularly sought for. In some cases, also, their outlines were so indefinite that there might have been doubt as to their nature had they not been previously noted and confirmed microscopically. The lymph follicles in all cases were prominently white, but not enlarged, usually not more than 1 mm. in diameter. This picture of the fine white follicles with the scattered, indefinite haemorrhages was constant throughout the series, and we do not recall having seen it duplicated in any other condition. Prominence and especially enlargement of the follicles are very commonly seen in soldiers, both from our own observation and from that of others, and we have noted this condition particularly in pneumonic conditions, but never with the occurrence of haemorrhages of the type described. In a few cases which were undiagnosed before death a tentative diagnosis of trench nephritis was made on the appearance of the spleen alone, and in each case was substantiated by the results of further examination and by the presence of albumin in the urine.

Kidneys. The kidneys constantly showed to the naked eye only the most slight and indefinite changes. It was seldom that one could attempt even a guess at the nature of the disease from the gross examination of the kidneys alone. They were seldom enlarged, and the only change suggesting disease was a slight pallor and opacity of the cortical tissue. The cortex was seldom swollen or wider than natural. A few of the kidneys showed some congestion so that

the cortical vessels stood out as red streaks against a pale background. In some cases swelling of the glomeruli, causing them to stand out from the cut surface like minute glistening drops, was observed, an appearance which has been particularly noted by Captain Shaw Dunn. This change, however, was not constant in our series.

Haemorrhagic lesions were not infrequently seen elsewhere than in the spleen. Several cases showed petechial haemorrhages in the renal pelves. Two cases showed numerous subepicardial, and one case numerous subpleural petechiae. We were not able to demonstrate haemorrhage into the lung tissue macroscopically. Two cases showed large cerebral haemorrhages, one central and one superficial.

The heart was often considerably dilated when the lung involvement was extreme, and such cases showed venous engorgement of the abdominal viscera. In most cases congested lymph nodes were found at the roots of the lungs, and often in the mesentery. The brain in some cases showed moderate subarachnoid oedema.

Histological Pathology.

We feel it necessary, before going into a description of the microscopical findings in trench nephritis, to acknowledge our indebtedness to Captain Shaw Dunn, R.A.M.C., who has been one of the chief pioneers in this field, and as a result of whose work our attention was first directed to many of the changes described (largely personal communication). Our findings have almost entirely agreed with his, and are presented with the object merely of putting on record the results in an additional series of cases. We understand that Captain Shaw Dunn has in the press an exhaustive study on this subject, which, however, has not appeared at the time of writing.

Histological examination was carried out on material from twenty of the twenty-five autopsies. The organs revealing the most evident changes were the lungs, spleen, and kidneys, and they will be taken in that order.

Lungs. The lung tissue under the microscope constantly revealed a more or less extensive serous exudate into the alveoli, apparently a primary process. With this there was usually seen an inflammatory process of almost certainly secondary origin, consisting of a purulent bronchitis or bronchopneumonia, or sometimes areas of diffuse pneumonic consolidation were seen. In addition to these two processes there was also constantly noted an often considerable deposit of fibrin in the serum-filled air-cells. It was of course difficult sharply to separate these three processes. It was usually apparent that the bronchial inflammation was to be ascribed to a secondary infection, a view which was substantiated by the greater frequency and severity of the bronchial lesions during the season at which purulent bronchitis was prevalent. Also, it seems reasonable to assume that a lung in which the air passages are filled with fluid should be extremely susceptible to the entry and establishment of secondary infection. It was more difficult to decide whether the deposition of fibrin had

taken place as a part of the primary exudation or was to be ascribed to the secondary inflammatory process. We are inclined to the former view because of the diffuse distribution of the fibrin, and because in several cases we noted very extensive and widespread fibrin deposits with little or no purulent exudate. The fibrin was seen in the form of a layer lining the walls of the air-cells or infundibula (Fig. 1), or where more abundant forming solid, dense plugs (Fig. 13), as seen in lobar pneumonia. More rarely only a light network was seen (Fig. 14). There was no extensive purulent exudate apart from areas in direct relation to involved bronchioles or the occasionally noted areas of consolidation, but in some cases there were small numbers of leucocytes scattered through the whole lung tissue. They were sometimes very numerous within the capillaries. The picture presented by the serum-filled air-cells with a scanty fibrin network and scattered leucocytes often strikingly resembled that seen in the earlier stages of a lobar pneumonia, or again in the early stages of gas-poisoning (Fig. 14). Some cases showed within the alveoli considerable collections of large mononuclear cells of the endothelial type, or again the alveolar epithelium was swollen and desquamated, sometimes as a solid layer (Fig. 15).

Thrombi were frequently seen within the lung vessels. Thus a capillary in an alveolar wall might show a dense plug of fibrin with apparent occlusion (Fig. 2), or a looser collection of fibrin might be seen with only partial occlusion. These capillary thrombi were definitely more evident and abundant in the areas where the intra-alveolar fibrin deposits were most extensive, and once we could trace a strand of fibrin connecting a capillary thrombus with the fibrin layer in an air-cell. The arterioles and smaller arteries in several cases contained solid fibrin plugs (Fig. 16), never with complete occlusion. The venules, on the other hand, usually showed only masses of loose fibrin network in which numerous leucocytes were held, and not the more solid thrombi.

The bronchioles usually showed the lesions of a purulent bronchitis, often with extension of the process through the wall to the surrounding air-cells, producing a true bronchopneumonia.

Congestion varied in degree, but was not usually extensive save sometimes at the bases. In many cases a certain amount of diffuse haemorrhage into the air-cells could be demonstrated.

Spleen. Congestion was usually marked and in some cases was extreme. The change most evident under the microscope was the presence of the haemorrhagic areas, which were usually numerous. In addition to the haemorrhages noted in the gross there were usually many smaller ones (Fig. 20). The larger haemorrhages were characteristically indefinite in outline, but the smaller ones were sometimes very sharply defined. In a few cases the outlines of the larger areas were so indefinite that there was doubt as to whether we were dealing with haemorrhage or with areas of intense congestion. The haemorrhages showed no constant distribution, but the smaller ones were often more numerous in the neighbourhood of the follicles.

In twelve cases of the series fibrin thrombi were demonstrated within the vessels. These were quite similar to those seen in the lung—those in the arterioles being usually solid, while those in the venules or pulp sinuses showed only a loose fibrin network with many leucocytes (Fig. 18). In eight cases we also noted what at first sight seemed to be an extensive fibrin deposit within the lymph follicles, occurring in the form of a heavy network becoming thicker or confluent at the centre of the follicle, or again forming a garland around the centre of the follicle as seen in cases of amyloid deposit (Fig. 19). With the stain used (Mallory's eosin-methylene blue) this material took a deep purplish red stain similar to fibrin, and moreover retained the stain when prepared by the Weigert method. We think, however, that it was more probably of the nature of amyloid than fibrin.

Polymorphonuclear leucocytes throughout the spleen pulp were always more numerous than normally, and sometimes were very abundant (Fig. 17). Thus, as compared with the spleens from cases of lobar pneumonia and of cerebro-spinal fever, most of the nephritis spleens showed at least as many leucocytes. They were often very numerous about the haemorrhages. Many large, hyaline, mononuclear cells were seen in the sinuses, and also large eosinophil cells and pigment-bearing cells. The lymph follicles were not definitely enlarged.

Kidney. The most evident and constant changes noted in the kidney were those seen in the glomeruli. These were characteristically larger than natural and often definitely swollen, and constantly showed an increase in the number of nucleated cells, with a marked decrease in the red blood-cell content (Figs. 7, 21, 24). The increased cellularity was observed to be due to at least three types of cells. The cells of the vascular endothelium were characteristically large and swollen, much decreasing the area of the capillary lumina (Fig. 22). The lumina, further, were usually filled with large, free, mononuclear cells, and with polymorphonuclear leucocytes. The nuclei of the vascular endothelium were large and vesicular, often lobulated, and sometimes suggesting amitotic division. No mitoses were seen. The large free cells noted usually showed nuclei of the same type, and seemed to have arisen *in situ* from the endothelium (Fig. 22). Occasionally free cells were seen with large, very irregular, densely solid-staining nuclei. The leucocytes were often numerous, making up, sometimes, as much as a fifth of all cells seen in a section of a glomerulus (Fig. 10). It was not uncommon to find a glomerulus in the section of which not a single red blood-cell could be seen.

The epithelium covering the glomerular tufts and lining the capsule often showed proliferation, particularly in the cases of longer duration (Fig. 9). Thus crescentic masses of desquamated epithelium might occasionally be seen. More commonly the capsule showed only swelling of the nuclei or some proliferation in a single layer. Leucocytes in some cases appeared in moderate numbers in the interstitial tissue surrounding the capsules.

A frequent appearance, and one which Captain Shaw Dunn considers as very characteristic, was the pouting or protrusion of the glomerular tuft into the

lumen of the convoluted tubule, presumably as a result of swelling and tension (Fig. 21).

In all the cases examined the tubular epithelium showed some evidence of degenerative change, but in only three or four cases was this of anything like advanced degree. In these cases the epithelium was swollen and granular, often obliterating the lumen, and sometimes detached from the basal connective tissue (Fig. 8). The nuclei showed chromatolysis and pyknotic changes. In a few cases the tubular epithelium was thin and atrophic, but still granular and showing considerable nuclear change (Fig. 21). Tube-casts were seen in most cases, but were never numerous. Very occasionally collections of leucocytes were seen within the convoluted tubules (Fig. 11). Haemorrhage into the tubules was seen in twelve of the twenty cases, and occasionally was seen to involve an entire kidney unit, filling the glomerular capsule and the entire tubule down to the main collecting tubules (Fig. 23). The haemorrhage probably always arose in the glomeruli since no intertubular haemorrhage was seen.

Mitoses were not infrequently seen in the cells of the convoluted tubules and loops of Henle (Fig. 12).

In nine cases definite fibrin thrombi were seen in the smaller arterioles (Fig. 3), and in eight of these occasional glomeruli showed solid thrombi in one or more capillary loops (Figs. 4, 5). The only evidence of infarction on a larger scale was found in one case where a small artery was completely thrombosed and the corresponding area of kidney tissue—about 2 mm. broad—infarcted and diffusely infiltrated with leucocytes (Fig. 6).

It is noteworthy that only four of the twenty cases showed changes of a chronic nature, and in only one of these of more than slight degree. It would appear, then, that in at least nineteen of the twenty cases the condition was acute and of recent origin.

Cases of Sudden Death.

In the series of cases on which post-mortem examination was performed there was a group which we think deserves special mention as being of considerable practical importance. These were the cases who were either found dead with no history of previous illness, or who died after only a very brief indisposition. As noted earlier, seven of the twenty-five autopsies recorded were on cases of this type. Summaries of five of these cases are given.

1. The patient had been indefinitely ill for three days, with some pyrexia, for which reason, on the third day, he was given Dover's powder. He died some few hours later, and the body was sent in for autopsy as a possible case of opium poisoning. Post-mortem examination revealed the lesions described in the preceding sections in very characteristic form, and the urine obtained from the bladder showed a large amount of albumin. Inquiry later elicited the fact

that the patient had shown, the day previous to death, what was apparently a uraemic convulsion.

2. The patient reported sick at morning sick parade. His temperature was 100° F., and he was sent back to his billet to rest. In the evening the temperature was the same. The next morning he was found dead in his bed. Autopsy showed characteristic lesions, and the urine contained a considerable amount of albumin.

3. The patient died following a wound which seemed much too slight to explain the fatal termination. Autopsy showed characteristic lesions of trench nephritis, and the urine showed a large amount of albumin.

4. The patient was admitted to a Casualty Clearing Station unconscious, the only history being that he had been in that condition for two or three days. He died shortly after admission, and the autopsy showed characteristic lesions, with a very large amount of albumin in the urine.

5. This case belonged to the class which are diagnosed as nephritis because the urine shows albumin, but which may show little or no indisposition—a type which was very frequent during the winter months. He was admitted to a Casualty Clearing Station and kept as a walking case for evacuation. On the fourth day he suddenly became very ill, with extreme dyspnoea and cyanosis, and died within twenty-four hours. This case at autopsy was one of the most characteristic of the entire series, the lung oedema and the spleen haemorrhages being very pronounced, as were also the histological changes in the kidneys. The urine showed a large amount of albumin.

Bacteriological Examination.

Bacteriological examination was carried out on material from sixty cases taken during life, and from sixteen of the series of twenty-five autopsies.

Blood. Blood cultures were made on a series of ten cases, all in the early stages of the disease, and all showing pyrexia. The blood was taken into veal infusion broth and incubated for ten days with daily examination. One case yielded an organism which was apparently a pneumococcus, growing in short chains with definite capsules, producing characteristic colonies on blood-agar, and fermenting inulin. It was of very low virulence for mice, and was only slightly bile-soluble, though the latter test was not conclusive as it was only applied three weeks after isolation. The presence of this organism in the blood was probably secondary to a pneumonic process in the lung. The cultures in the remaining nine cases remained sterile.

Urine. In a series of forty cases cultures were made from the urine, the technique employed in most cases being as follows: the glans penis was swabbed off with sterile salt solution and the patient then passed the first part of his urine into the urinal, the last portion being taken into a sterile tube. 2 to 3 c.c. of this urine were then added to a tube of veal infusion broth or of heart trypsin

broth. This was plated on blood-agar after twenty-four hours, and again after forty-eight hours if the first plate did not yield the type of colony sought.

In twenty-four of the forty cases the urine yielded streptococci of the enterococcus or faecal type. These organisms produced a luxuriant, confluent, often opaque growth on serum-free agar—sometimes simulating a staphylococcus—and on blood-agar produced colonies up to 1 mm. in diameter, rather opaque by transmitted light, with a narrow green halo, and by reflected light often whitish, the halo then appearing as a blackish background to the colony. Under the microscope they showed short chains of often elongated cocci. In most of the cases haemolytic streptococci were present as well.

The urine from a series of fifty control cases was then examined. These embraced many conditions, the diagnoses including diarrhoea, trench fever, pneumonia, cerebro-spinal fever, scarlet fever, trench feet, and several others. In only five of these cases were streptococci isolated which produced a green colour on blood-agar. Of these three were quite different from the enterococcus type, growing in tremendously long chains. The remaining two organisms seemed to belong to the class described above. One of them was obtained from a case of diarrhoea. The other was recovered from the urine, taken at autopsy, of a case diagnosed clinically as nephritis, and showing post mortem extensive chronic lesions in the kidneys. This case, we think, after consideration of the histological changes, was probably terminally a case of trench nephritis, although it is not included in the series described. Most of the control urines yielded haemolytic streptococci.

Throat cultures. In twelve cases ascitic broth tubes were inoculated with swabs from the throat, and plated on blood-agar after twenty-four hours' incubation. The cultures from ten of these cases yielded streptococci producing fine dryish colonies on blood-agar, with a pronounced green halo, and growing scantily in subculture on solid media. Several cases also yielded pneumococci. In no case was an organism of the enterococcus type recovered. None of these organisms appeared to be of the type described by Mair as present in the throats of scarlet fever patients. We also failed to recover such organisms by injecting the ascitic broth cultures into mice as he recommends.

Post-mortem cultures. In sixteen cases cultures were made at autopsy from heart blood, lungs, spleen, and kidneys, the organs being punctured with glass pipettes after searing the surface. These were all cases in which autopsy was performed within a very few hours after death.

Of the sixteen cases, in nine cases streptococci were isolated from the lung, in six cases from the spleen, and in two cases from the kidney. Cultures from heart blood remained sterile in every case.

The streptococci from the lung were all of the type described as recovered from the throat cultures, and were never of the enterococcus type. The organisms isolated from the spleen and kidney, on the contrary, were in general similar to those found in the urine of nephritis cases, and may be considered as

enterococci. In one of the two cases in which such an organism was isolated from the kidney a similar streptococcus was recovered from the spleen also, and in this case streptococci could be demonstrated in the tissues.

During the season at which influenza was prevalent influenza bacilli were isolated from the lungs of two cases and from the kidney of a third.

Sugar reactions. A series of sixteen cultures of green streptococci from cases of trench nephritis were tested against lactose, mannite, salicin, inulin, and raffinose, with the results noted below. The two urine organisms from the control series, and a culture of Houston's enterococcus, for which we are indebted to Captain Dible, R.A.M.C., were also tested. The organisms from nephritis cases fell into three groups as regards fermentation, while the streptococcus from the case of diarrhoea differed from the others in fermenting raffinose.

	Fermentation.					Source of Cultures.				
	Lactose.	Mannite.	Salicin.	Inulin.	Raffinose.	Urine.	Throat.	Lung.	Spleen.	Kidney.
(1)	Ac.	Ac.	Ac.	0	0	3	1	1	1	1
(2)	Ac.	0	Ac.	0	0	2	—	—	1	—
(3)	0	Ac.	Ac.	0	0	6	—	—	—	—
	Ac.	Ac.	Ac.	0	Ac.	Organism from urine of case of diarrhoea.				

The streptococcus from the urine of the case of chronic nephritis and the culture of Houston's enterococcus both gave the reactions of group (1).

Pathogenicity. Broth cultures of three organisms from the urine, three from the throat, and one from the spleen were injected subcutaneously into mice, the dose being 1 c.c. All the animals died in from three to five days, but in no instance could the streptococci be recovered from the blood or organs. One rabbit was injected intravenously with a large dose of a saline emulsion of a urine streptococcus, and another with a similar dose of a recently isolated streptococcus from the spleen. The latter animal developed paresis and cachexia during the third week, as has been described for the enterococcus, but the organism could not be recovered post mortem. The other rabbit remained healthy. Neither showed albuminuria, the urine being examined daily.

Examination of tissues. Sections from lungs, spleen, and kidneys, of all cases examined histologically, were searched for organisms, using both the eosin-methylene blue stain and the Gram-Weigert method. In one case all three organs showed the presence of cocci in pairs and chains of two or three pairs. These cocci were diffusely distributed, and collections of them were never found. All the other tissues examined yielded negative results, save that cocci were sometimes found in the bronchioles of cases showing severe bronchitis.

Discussion.

We have briefly described the picture seen in the early stages of trench nephritis, as based on the clinical observation of a series of 150 cases. The great majority of these showed marked respiratory symptoms and oedema of the face and extremities, and only one case showed evidence of uraemia, though we believe the true proportion of uraemic cases in the disease to be considerably higher than our figures represent. The onset, in our cases, was characterized by pallor, dyspnoea, and anasarca, with often a history of cough, and the previous history was strikingly devoid of any evidence of predisposing disease. Many of our cases were complicated by severe bronchitis, which much increased the respiratory distress, and which undoubtedly was an important factor in the fatal cases. The mortality in a series of 113 cases was 4 per cent. In about three-quarters of all cases improvement was rapid under rest, purgation, and symptomatic treatment.

Although the extensive oedema and the albuminuria suggest derangement of renal function, the quantity of urine passed was often close to normal, and, save in the one uraemic case, never greatly diminished.

We have no reliable figures on the occurrence of acidosis in this series, but we do not believe that it was the most important direct cause of the dyspnoea. We consider, from both clinical and pathological evidence, that the dyspnoea, at least in the early stages, was the result of the mechanical interference with lung function produced by the pulmonary oedema, but it was certainly greatly increased by the complicating bronchitis.

We have noted a group of cases which died suddenly after indisposition of insignificant degree and duration. From autopsy findings and from the urine examination we believe these to have been cases of trench nephritis. These cases are emphasized as showing that this type of nephritis must be added to the list of conditions that are to be kept in mind when considering a case of sudden illness or sudden death.

The appearances noted at autopsy formed a fairly characteristic and constant picture, the diagnosis being in nearly all cases at least probable, and often undoubted. The most characteristic lesions were those of the lungs and spleen, and those in the latter organ were, in our opinion, of considerable diagnostic value.

Discussion as to the primary cause of the disease must remain more or less futile until we have in our possession much more abundant and more accurate data than at present. Many of the writers on the subject give lists of possible etiological factors. These fall roughly into the three classes, *infective*, *dietetic*, and *toxic*, and some of the writers range themselves more or less definitely behind one or the other theory. The divergence of views would indicate, and indeed it must be obvious to any one acquainted with the results of investigation of the disease up to date, that we are as yet far from a knowledge of the cause of trench nephritis. We cannot correlate, to more than a slight degree, the

clinical manifestations with the changes found post mortem, or even say with certainty which lesions are to be considered primary and which secondary. In the present paper we have purposely avoided the expression of an opinion as to the primary etiology, and confine ourselves, in discussion, to speculation upon the significance of the more evident pathological changes.

The most evident lesions, and those offering the most extensive field for such speculation, are undoubtedly those occurring in the lungs. We have noted that these seemed to be the results of two separate processes—a primary, diffuse, exudative process, and a secondary, infective bronchitis. We have also noted that the extensive oedema of the lungs showed certain characteristics which are lacking in the oedema of ordinary nephritis, namely, the deposition of a considerable amount of fibrin (Figs. 1, 13, 14), sometimes a scanty, diffusely scattered, leucocytic exudate, swelling and desquamation of the alveolar epithelium (Fig. 15), and collections of mononuclear 'catarrhal cells'. These findings indicate more than a simple oedema, they point to a local irritant process. We have said that clinically many cases strongly resembled certain cases of gas-poisoning, and that the analogy was often very striking at autopsy and histologically. This analogy led Captain Shaw Dunn, early in his work on the disease, to the idea that the causative agent might be inhaled gas or fumes of some sort. The occurrence of many cases in areas where such accidents could be excluded has rendered this hypothesis untenable, but the analogy still remains. Discarding the idea of an inhaled chemical irritant, there remain at least two types of bodies which might conceivably give rise to such a condition—excreted toxic products and infective agents. It is to be noted that in only one case in our series were organisms demonstrated in the lung tissue apart from the bronchial lesions. When it is remembered that in the common pneumonic infections bacteria can usually be readily found, it would seem that the lung condition in trench nephritis, if of infective origin, is not due to any of the ordinary lung invaders. We do not attempt to discard entirely the more obvious explanation of the lung oedema as being part of the general oedema, but we wish to emphasize that there is evidence of there being added to this an irritant process of as yet unexplained origin. We feel also that the explanation of this process would have a very important bearing on the etiology of the disease.

The purulent bronchitis we consider to be a secondary infection implanted on a serum-filled lung. This view is substantiated by the seasonal incidence of the bronchitis in nephritis patients, and by the isolation from the lungs of streptococci of the mouth type. The bronchitis is, however, of great practical importance, and in many fatal cases it undoubtedly contributed largely to the outcome.

The origin of the thrombi seen within the vessels of the lungs, spleen, and kidneys remains as yet uncertain, but we believe that they arise mainly in the lung, and that their formation represents a phase of the irritant process outlined. Thus the capillary thrombi were more numerous in the parts of the lung where the intra-alveolar fibrin deposits were most extensive; and further, we once

found a capillary thrombus connected by a strand of fibrin with the fibrin mass within an air-cell—much as in lobar pneumonia the fibrin network in contiguous air-cells may be continuous through the alveolar wall. We believe that the larger solid thrombi seen in the arterioles of various organs arise from cast-off portions of these capillary thrombi, although we cannot explain why definite infarcts should not then be found more frequently. We have noted in one case the complete occlusion of a kidney arteriole with the production of an infarct (Fig. 6). Captain Shaw Dunn has already expressed a similar view as to the formation of the disseminated thrombi. We have noted a suggestive analogy in the spleens of a few cases of lobar pneumonia, where we have found thrombi of the same appearance as those seen in the nephritis cases.

The loose thrombi seen in the venules seemed to be of ante-mortem origin, since they often contained large numbers of leucocytes and no red blood-cells. It is possible, however, that sedimentation may account for this, and in any case their formation was probably not earlier than the terminal stage (Fig. 18).

The capillary thrombi seen in the kidney glomeruli may come from the lung, but the possibility must be considered of their having arisen *in situ* (Figs. 4, 5). The tissue changes described in the glomeruli suggest a local inflammatory process affecting the vascular endothelium (Fig. 22), and indeed some writers think that a generalized endarteritis occurs. We have not seen evidence of such a process save in the glomeruli.

In a few cases in which the coagulation time of the blood was estimated we were unable to detect an increase in the rate.

We have not been able to demonstrate a relationship between the thrombi and the spleen haemorrhages, but it is difficult to discard the idea that such a connexion exists. The other haemorrhagic lesions noted were in general similar to those seen in asphyxia, and it is probable that they are of identical nature, since air-hunger is a predominating symptom in the severe cases.

The kidney lesions described, while constant and, in our opinion, characteristic, seemed much less advanced than might have been expected from the severity of the symptoms, and particularly of those symptoms which are by custom ascribed to renal derangement. While the glomerular changes are constant we cannot consider them specific, for we have seen in fatal cases of lobar pneumonia, showing no renal symptoms, almost identical appearances in the glomeruli.

The bacteriological results we cannot consider to have an important etiological bearing on the disease. Organisms of the enterococcus type have been isolated in several other diseases, but the case against them as a primary cause has always been very weak. Moreover, the streptococci which we isolated seemed, from the sugar reactions, to comprise at least three or four types. We think, however, that the finding of such organisms in the urine of nearly two-thirds of the nephritis cases examined, and their almost complete absence in a larger control series, entitles them to consideration if only for the purpose of explaining their presence. It seems probable that they come originally from

the bowel, and two explanations for their frequent isolation from the urine in trench nephritis occur to us. The bowel may be rendered more permeable to this type of organism, much as in animals, after injection of foreign protein, intestinal bacteria may be found in the blood-stream. Or again they may be normally excreted in the urine in small numbers, and in the presence of the albuminous material may be enabled to multiply so that they are more easily found in cultures of the urine. Assuming these streptococci to be not primarily concerned in the disease, we still think it conceivable that they may have an importance in the production of some of the lesions. For example, according to one writer, the kidneys of rabbits injected with cultures of streptococci may show glomerular changes of much the same order as those seen in trench nephritis.

During the course of the work described in this paper the impression has constantly grown upon us that the features presented by this disease are such as to lead to a doubt whether a kidney lesion is really at the basis of the condition, in spite of the fact that some of the symptoms are the same as those seen in the nephritis of civil life. We have attempted to suggest, in the foregoing description, the importance of the pulmonary lesions, both from the clinical and from the pathological standpoint, as evidenced by the predominance of the respiratory symptoms and by the peculiarity of the changes found in the lungs. We may say, also, that the impression received from personal observation was much stronger than can be conveyed by the written description of our observations. Although the data which we present in this paper are in no sense conclusive, we suggest this view of the disease in order to point out the necessity of investigation from other standpoints than those usually adopted in dealing with nephritis.

We have not been able, under the circumstances, to give complete references to the published reports on trench nephritis, and we have therefore not attempted to present any general survey of the literature, but have confined ourselves to acknowledging the personal assistance received from two or three workers. We are indebted to Dr. William Mair of the Lister Institute for the examination of a number of streptococci, and for a gift of material. We wish also particularly to thank Captain Adrian Stokes, R.A.M.C., for a great deal of practical assistance, and for many valuable suggestions.

DESCRIPTION OF FIGURES.

All tissues of which photomicrographs are reproduced were fixed in Zenker's fluid, and stained by Mallory's eosin-methylene blue.

PLATE 1, FIG. 1. Lung. Fibrin layer on wall of infundibulum. The dark masses seen lying in the wall beneath the fibrin are capillary thrombi. × 215.

FIG. 2. Lung. Solid thrombus in capillary of alveolar wall. × 480.

FIG. 3. Kidney. Solid thrombus in small arteriole. × 560.

FIG. 4. Kidney. Solid thrombus in glomerular capillary. × 950.

FIG. 5. Kidney. Solid thrombus in glomerular capillary. × 950.

FIG. 6. Kidney. Complete thrombosis of small artery. The corresponding area of the cortex was infarcted. × 60.

PLATE 2, FIG. 7. Kidney. Glomerulus showing increased cellularity. × 180.

FIG. 8. Kidney. Acute degenerative changes in convoluted tubules. × 160.

FIG. 9. Kidney. Capsular proliferation. × 440.

FIG. 10. Kidney. Polymorphonuclear leucocytes in glomerular capillaries. × 950.

FIG. 11. Kidney. Polymorphonuclear leucocytes in convoluted tubule. × 440.

FIG. 12. Kidney. Mitotic figure in cell of a convoluted tubule. × 440.

PLATE 3, FIG. 13. Lung. Serum-filled air-cells with massive fibrin deposits and sparsely scattered leucocytes. × 75.

FIG. 14. Lung. Light fibrin network with a few scattered leucocytes, simulating the appearance seen in early pneumonia or in early gas-poisoning. × 215.

FIG. 15. Lung. Swelling and commencing desquamation of alveolar epithelium. Note the leucocytes in the capillaries and the solid fibrin masses in the air-cells. × 480.

FIG. 16. Lung. Large solid thrombi in small artery. × 35.

FIG. 17. Spleen. Shows the large proportion of polymorphonuclear leucocytes in the spleen pulp, lying both in and between the sinuses. × 480.

FIG. 18. Spleen. Loose fibrin mass in large venule, containing numerous leucocytes, but almost no red blood-cells. × 480.

PLATE 4, FIG. 19. Spleen. Lymph follicle with deposit resembling amyloid. × 215.

FIG. 20. Spleen. Shows small irregular haemorrhages. We were not able, with the apparatus at our disposal, to reproduce the larger haemorrhages which give the characteristic appearance in the gross. × 35.

FIG. 21. Kidney. Glomerulus showing increased cellularity and numerous polymorphonuclear leucocytes. Note the pouting of the tuft into the commencement of the tubule, and also the thin atrophic epithelium of the neighbouring tubules. × 260.

FIG. 22. Kidney. Glomerular tissue showing swelling and multiplication of vascular endothelium. Note that many of the cells lie free in the capillary lumen. × 950.

FIG. 23. Kidney. Haemorrhage into glomerulus and filling the entire convoluted tubule. × 60.

FIG. 24. Kidney. Glomerulus showing increased cellularity. × 350.

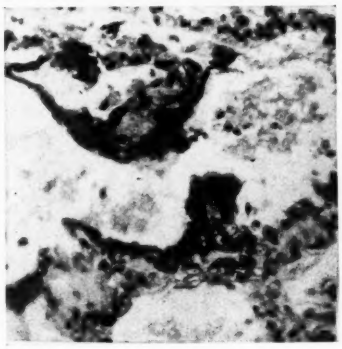


FIG. 1

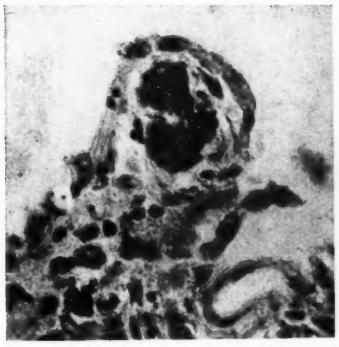


FIG. 2

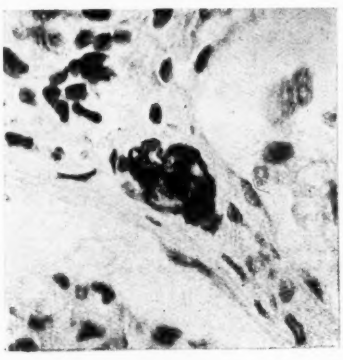


FIG. 3

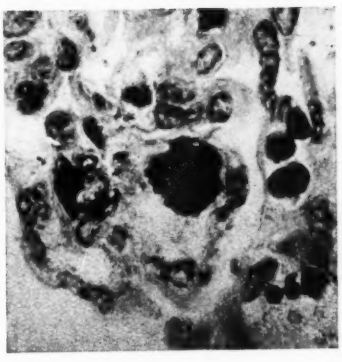


FIG. 4

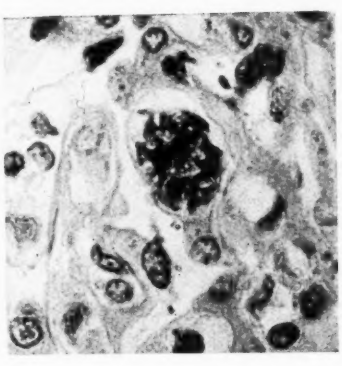


FIG. 5

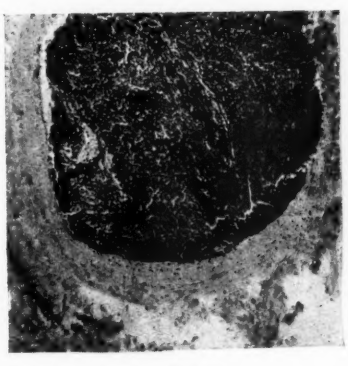


FIG. 6

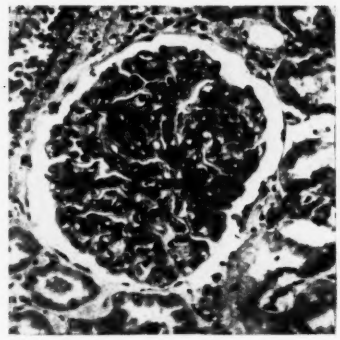


FIG. 7

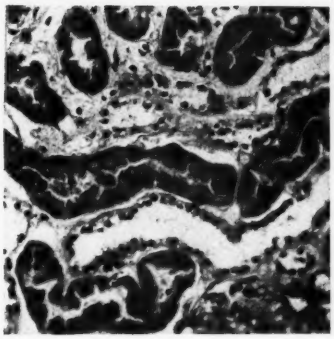


FIG. 8

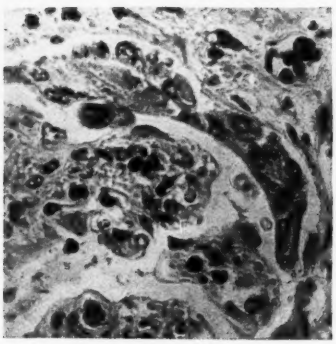


FIG. 9

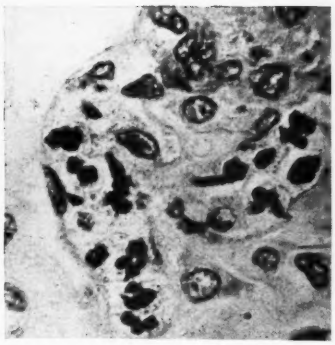


FIG. 10

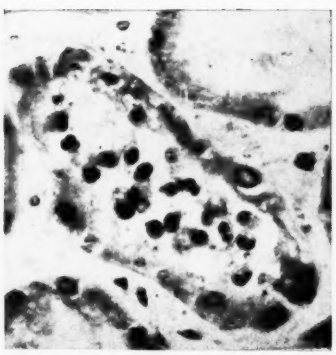


FIG. 11

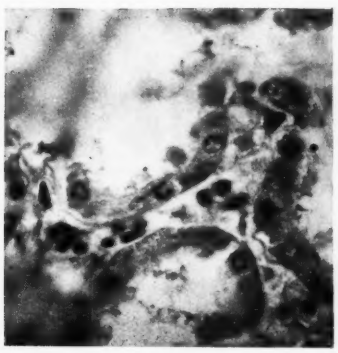


FIG. 12

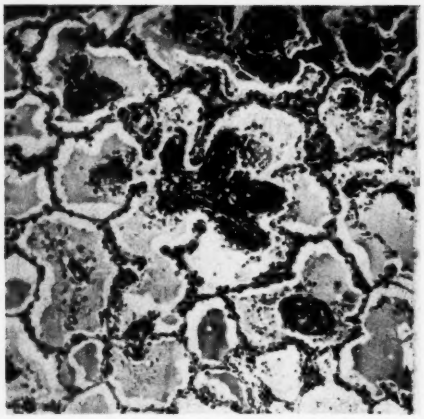


FIG. 13

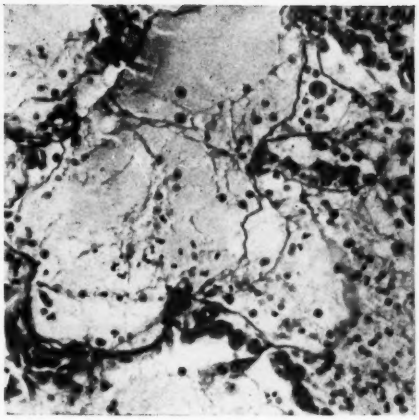


FIG. 14

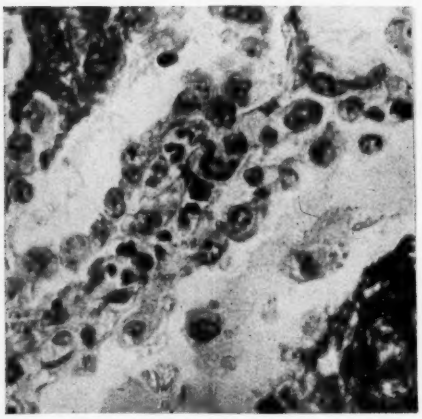


FIG. 15

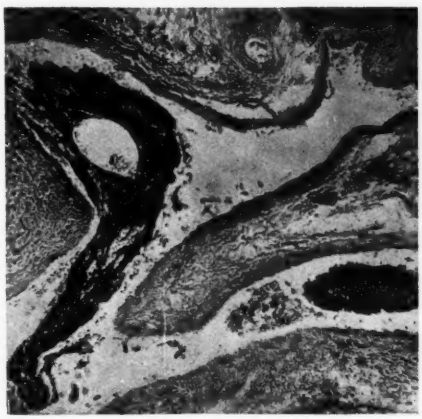


FIG. 16

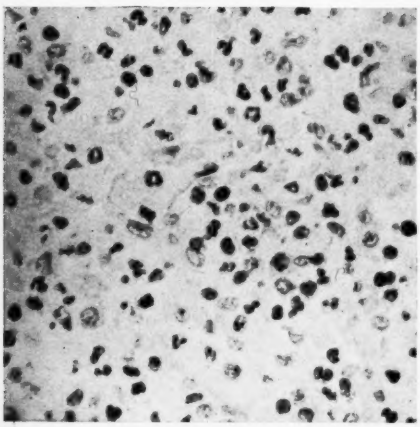


FIG. 17

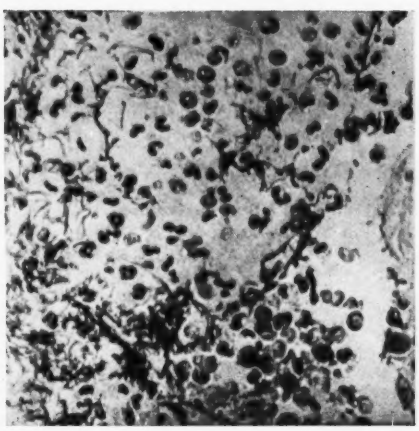


FIG. 18

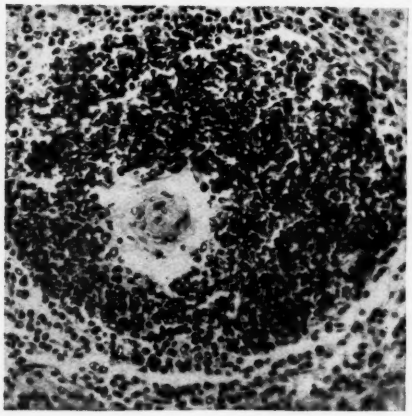


FIG. 19

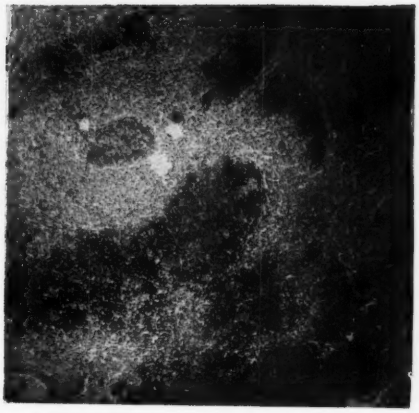


FIG. 20

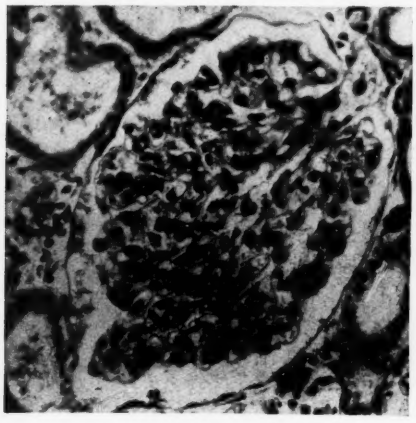


FIG. 21

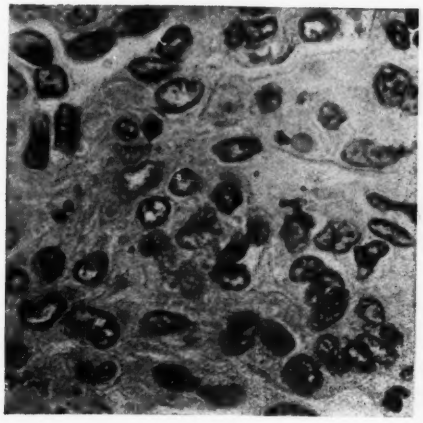


FIG. 22

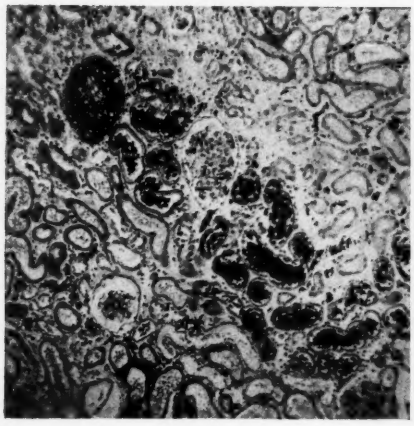


FIG. 23

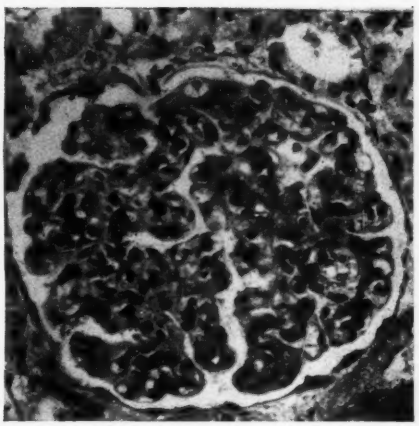


FIG. 24

OBSERVATIONS IN SIX CASES OF PAROXYSMAL TACHYCARDIA

By W. E. HUME

With Plates 5–7

TACHYCARDIA is common amongst soldiers who have been sent to the Base with the diagnosis of 'D. A. H.' or 'V. D. H.' In most cases the rapid heart action is a simple tachycardia with a normal rhythm, and has none of the special features which distinguish a true paroxysmal tachycardia. Amongst 2,400 patients sent with a diagnosis of 'D. A. H.' or 'V. D. H.' six cases of paroxysmal tachycardia have been discovered. They present certain interesting features in that in all of them there was an absence of other signs of organic heart disease, the paroxysms were readily induced by exertion, and the exciting focus in the heart seemed to lie in the ventricular musculature. In order to discover the immediate cause of the attacks, certain observations were made on the nervous system, on the posture of the body, and on various drugs. For instance, the vagus was stimulated by pressure in the neck and its inhibitory action was removed by the paralysis of its nerve-endings by atropin; the sympathetic system was excited by the intravenous injection of adrenalin chloride. Changes in posture were utilized in an endeavour to ascertain the varying effects of venous pressure, and amyl nitrite was administered by inhalation in order to discover the effect of lowering the peripheral arterial pressure.

In all cases polygraphic records were obtained, and I was enabled by the kindness' of Capt. McIlwaine, R.A.M.C., to obtain electro-cardiographic records in three of my patients.

Case I, aged 20, was admitted to the convalescent camp on Jan. 20, 1917, and gave the following history. He had been 10 months in the Army and had spent 5½ months in France. Four years previously he had had diphtheria, and during convalescence he began to suffer from attacks of palpitation, which were frequent during the following year. He sought the advice of many doctors, who told him there was nothing seriously amiss with his heart and that he would outgrow the attacks, the nature of which was apparently not detected. During the next three years the attacks were less frequent, and at the time of enlistment he felt well. He stated that he managed to support his training in England, though he had occasional attacks of palpitation. During the two months previous to his admission to the convalescent camp the attacks had again become more frequent, and as he had reported sick with them on two or three occasions he had been given the lighter work of a signaller.

Previous health and habits. Beyond the attack of diphtheria four years previously, he had been perfectly healthy, and at the time of enlistment he was

attending the courses of an agricultural student. There was no history of scarlet fever or rheumatic fever.

On examination. A small, fresh-coloured individual, he was in no way nervous or alarmed by the occurrence of the attacks. On examination of the heart there was no enlargement and no murmurs could be detected. At rest there was a slight sinus irregularity; the pulse-rate varied from 70 to 80 at complete rest, and when going about the rate increased to 114. At times he complained of pain in the region of the heart on exertion.

The attacks. Attacks of paroxysmal tachycardia were easily caused by exertion, such as a sharp run or quick marking time. Sometimes a sudden movement, such as stooping to pick something from the floor, would bring on an attack.

The onset of the attack was quite abrupt, and during it he lay down and his face became slightly pale. Respiration was slightly increased and he was conscious of the rapid beating of the heart, complaining of considerable praecordial discomfort. The attack usually lasted fifteen to twenty minutes, though at times it would last as long as two hours. The end always came abruptly, and in one beat the normal rhythm was restored.

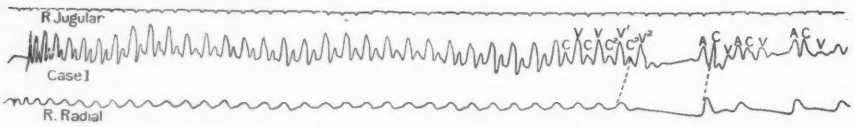


FIG. 1. Case I. End of attack of paroxysmal tachycardia. Two waves C and V are found in jugular tracing. To the right of the figure a normal A, C, V sequence is found.

Records were taken in many attacks, and Fig. 1 shows the termination of a paroxysm. The attack ends suddenly, and the last three groups of the venous pulse denote a normal A, C, V complex. In each cardiac cycle there are two waves in the jugular pulse which have been marked C and V. It is always difficult to be certain of the interpretation of a tracing of the venous pulse when the heart is beating rapidly, and various interpretations might be given of Fig. 1. If the last two complexes of the paroxysm are considered, the hypothetical position of the wave A may be argued. There is no evidence of a separate A wave, but it may be buried in either C or V. If buried in C a larger wave than that which occurs might have been expected, had the auricular and ventricular contractions occurred at the same moment. The simultaneous contraction of auricle and ventricle almost invariably gives rise to a single large wave in the jugular tracing. The A wave may lie buried in V, and this leads to two further interpretations. Therefore, secondly, the tachycardia may be of auricular origin: in this case the A wave, denoting auricular contraction, which governs C^1, must be buried in V, and the A wave of the auricular contraction, which governs C^2, must be buried in V^1. If this is the correct interpretation of the venous pulse a difficulty arises as to why there is no wave C^3, evidence of ventricular contraction, following the auricular wave which is assumed to be buried in the wave V^2: in this case it must be concluded that there is no ventricular response to this auricular contraction. Thirdly, the explanation may be that there is a retrograde stimulation of the auricle from the ventricle, and it must then be assumed that the A wave which immediately follows C^1 is buried in V^1, and that the A wave which corresponds to C^2 is buried in V^2. Three interpretations, therefore, have been given of this venous pulse. Firstly, by a simultaneous contraction of auricle and ventricle giving rise to a single wave C. The smallness of the C wave makes this interpretation unlikely. Secondly, an A wave may be buried in the V waves preceding each C wave, assuming an auricular tachycardia. Thirdly, that the A wave of each complex follows the

corresponding C wave, assuming a retrograde stimulation of auricle from ventricle. A fourth possibility may be that the auricles are in a condition of fibrillation and that the ventricles are contracting regularly from an abnormal focus in their own musculature. Plate 5 is an electro-cardiogram of this patient and shows the complexes in leads I, II, III.

In lead I R, S, T complexes are well marked, and in leads II and III R and T are alone prominent. It is impossible to identify a P wave. The ventricular complexes have the form usually associated with premature beats arising in the right and basal portion of the ventricular musculature. It will be most convenient to discuss the characters of this electro-cardiogram after the consideration of the other cases. In the meantime, attention may be drawn to the fact that we are apparently dealing with a ventricular form of venous pulse, and with ventricular complexes in an electro-cardiogram which suggest an origin from below the auriculo-ventricular junctional tissues.

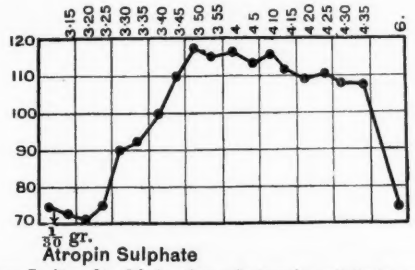


CHART I. Case I. Result of injection of atropin sulphate gr. $\frac{1}{30}$. Numerals to the left indicate pulse-rates. Figures above indicate time.

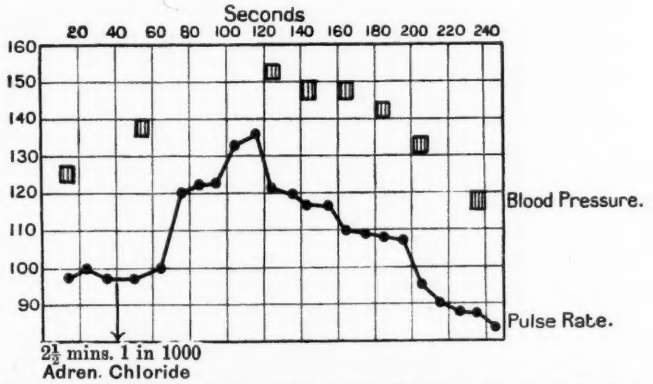


CHART II. Case I. Result of injection of adrenalin chloride. Figures to the left indicate pulse-rates and blood pressures.

Causation of the attacks. The attacks were easily caused by exertion, such as running or quick marking time, or by some sudden movement. As there was no obvious valvular or muscular lesion it seemed advisable to investigate the influence of the peripheral nervous system. The considerations which led to this investigation were the following: It seemed possible that either the removal of the vagal control of the heart or the direct stimulation of the sympathetic nerve might determine an attack. In order to remove the inhibitory influence of the vagus $\frac{1}{30}$ gr. atropin sulphate was administered hypodermically and Chart I shows the result. No paroxysm was produced as the result of complete removal of the vagal control, and the reaction was in every

way normal. In order to directly stimulate the sympathetic nervous system $2\frac{1}{2}$ minims of a 1 in 1,000 solution of adrenalin chloride were injected into the median basilic vein of the arm. Chart II shows the result of the injection. The heart-rate increased from 100 to 135 after $\frac{1}{4}$ minute and then gradually slowed to normal in $2\frac{1}{2}$ minutes, and the blood-pressure increased from 125 mm. Hg to 150 mm. Hg. This is a perfectly normal reaction, and the stimulation of the sympathetic nerve to the heart did not produce a paroxysmal tachycardia.

Vagus in the neck. During an attack the vagus was pressed in the neck, but all degrees of pressure were without influence on the rate of the paroxysm, and the eyeball was also pressed without any influence on the rate of the heart. Both these methods of stimulating the vagus produced marked slowing of the heart when it was beating with a normal rhythm. During an attack the abdomen was heavily pressed in an endeavour to drive the blood from the abdomen into the thorax and in this way to assist the filling of the right auricle. On one occasion the paroxysm stopped momentarily, to be continued after two normal beats, and on another occasion it ceased altogether. There were occasions, however, when no effect could be produced by this means.

Alterations of posture were tried, the head and trunk being placed at a lower level than the legs, but this manœuvre did not apparently affect the rate.

The patient himself had said that sometimes he could bring an attack to an end by suddenly stooping, and on one occasion, after all the above methods to terminate a paroxysm had been tried, he stooped to fasten his bootlace and the attack immediately ceased. This patient was eventually discharged to England.

Case II. This patient, aged 24, was sent to the convalescent camp with the diagnosis of D. A. H. He had been complaining of palpitation for three weeks. Three weeks previously a shell burst near him and immediately his heart seemed to race, and since that time he had had short attacks of palpitation and was short of breath.

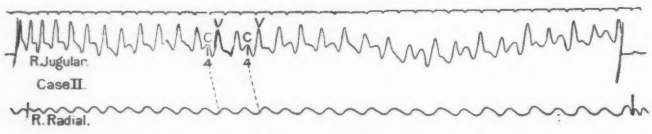


FIG. 2. Case II. Attack of paroxysmal tachycardia. In the jugular tracing are two waves, C and V.

On examination no abnormality in the size or the sounds of the heart could be detected, the rate was 104, and the rhythm was normal. He was a golf-groundsman in civil life and had managed his training all right. After admission to the convalescent camp he suffered from attacks of paroxysmal tachycardia. He was seized with the first attack while he was engaged in sweeping the floor in a Y.M.C.A. hut; he stooped suddenly and felt that his heart began to beat fast and he became giddy. During his stay in the camp he had four similar attacks. The second paroxysm seemed to occur after a deep sighing inspiration, while he was sitting on his bed quietly reading. The third occurred after having awkwardly thrown himself on to his bed, and the fourth and fifth began after a sudden stooping movement. He had not discovered any method of bringing a paroxysm to an end. Besides the five attacks which came on spontaneously, attacks could usually be brought on by exertion, such as running fifty yards, and many paroxysms induced in this way were studied. Fig. 2 is a polygraphic tracing of a paroxysm. As in Case I, there are two waves in the jugular pulse and the same arguments for the interpretation of the waves hold in this case. Unfortunately there was no opportunity of obtaining an electro-cardiogram in this case. As in Case I, the same observations were made on the influence of

the nervous system and posture, on the mechanism by which the attacks might be produced or could be caused to cease.

$\frac{1}{50}$ gr. atropin sulphate was injected hypodermically and the rate increased from 82 to 105 in less than one hour, but the release of the vagal control did not produce a paroxysm. $2\frac{1}{2}$ minims of a 1 in 1,000 solution of adrenalin chloride caused the usual quickening of the heart and increase in blood-pressure, but this stimulation of the peripheral sympathetic nerves did not bring on an attack. Various endeavours were made without avail to stop the paroxysms—such as by vagal pressure in the neck, pressure upon the eyeball, the swallowing of cold water, and alterations in posture. Both pressure upon the right vagus in the neck and upon the right eyeball slowed the heart, when beating with a normal rhythm, by some 15–20 beats per minute, but both methods were without any effect upon the rhythm or rate of the paroxysm. Neither pressure upon the abdomen nor any alterations in posture made any difference in the rate of the tachycardia.

Case III. This patient had complained of palpitation after exertion for twenty-one months, but he had not reported sick until six days before admission. The attacks of palpitation had not been severe, though at times he had been

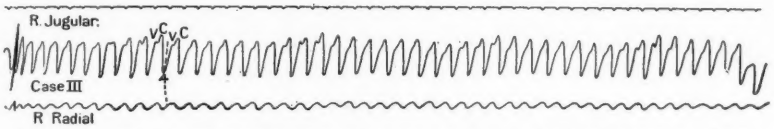


FIG. 3. Case III. Attack of paroxysmal tachycardia. In the jugular tracing there is a single wave, at times with a bifid apex.

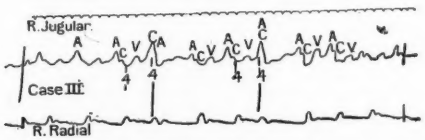


FIG. 4. Case III. Jugular and radial tracings both show premature ventricular contractions (2).

incapacitated by the accompanying giddiness. He had had an attack at intervals of two to three weeks, which had usually lasted about two hours. Six days before admission, while eating his supper, he stated that he had become suddenly blind and that his heart began to beat very violently. Before enlistment he had been a labourer and had enjoyed excellent health. On examination of the heart there was slight apical tenderness; the rhythm, size, and sounds were perfectly normal to the ordinary methods of examination. As in the two previous cases, the attacks could usually, though by no means invariably, be induced by exertion.

Fig. 3 is a polygraphic tracing from this case. The rate is approximately 265 per minute. There is usually a single wave in the jugular pulse, though at times the apex of the wave is broken into two parts.

Again there is a ventricular type of venous pulse, and the arguments which have been advanced in Case I are also applicable in this case. In the non-paroxysmal periods the normal A, C, V rhythm was frequently disturbed by the appearance of premature beats which arose from the ventricle. An example of this rhythm is shown in Fig. 4. This tendency towards an increased irritability of the ventricular musculature throws some light on the focus of origin of the paroxysm. Plate 6 is a galvanometric record of this case. As in Case I R, S, T complexes are distinct, but no P wave can be differentiated. The further discussion of the type of paroxysm in this case is discussed later.

On June 29, 1917, 2½ minims of a 1 in 1,000 solution of adrenalin chloride were injected into the median basilic vein, and Chart III represents the resulting quickening of the heart and the rise in the blood-pressure. The injection of adrenalin chloride did not produce an attack of paroxysmal tachycardia. A capsule of amyl nitrite was inhaled, and the rate of the heart was quickened from 78 to 150 beats per minute. The effect of the inhalation of oxygen and

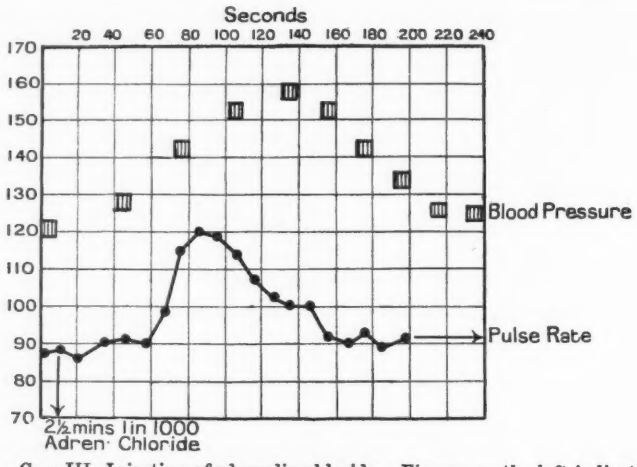


CHART III. Case III. Injection of adrenalin chloride. Figures on the left indicate pulse-rates and blood pressure.

carbon dioxide were also observed. After the inhalation of oxygen for five minutes the rate of the heart was increased from 64 to 66 beats per minute. After respiring his own breath (carbon dioxide) for two minutes the rate quickened from 68 to 76 beats per minute. None of these procedures caused a paroxysmal attack. $\frac{1}{30}$ gr. atropin sulphate increased the rate of the heart from 78 to 120 beats per minute, but did not produce an attack.

Case IV. Was admitted on June 1, 1917, and gave the following history. One year before admission he had an attack of palpitation after running a foot-race, and this attack lasted eight to ten hours. Since that time he had had similar attacks, which were said sometimes to continue for as long as eight days. He complained also of shortness of breath on exertion and of pain in the region of the heart during an attack of palpitation. In November 1916 he reported sick, his chief complaint being of palpitation, and he spent two weeks at a convalescent camp. On April 1, 1917, he again had to report sick, and was sent to the transport lines, where he had worked until admission to the camp on June 1, 1917. His civil occupation had been that of a farmer, and he had enjoyed perfect health previous to enlistment. On examination the heart was apparently normal to the ordinary methods of examination. There was no tenderness and the rate was 80. The rhythm was quite regular; there was no enlargement and the sounds were clear. As the history suggested that the palpitation might be due to attacks of paroxysmal tachycardia he was made to run fifty yards; on return it was obvious that an abnormal rhythm had been induced.

Fig. 5 is a record of the tracing. Unfortunately it was impossible to obtain a record from the radial artery, and the polygraphic tracing shows an inverted cardiogram. Again the venous pulse is of the ventricular type. Plate 7 is the electro-cardiogram of this patient. The R, S, T (ventricular) complexes in each of the three leads have the form of premature beats arising

from the right and basal parts of the ventricle. Lead II is quite characteristic of this type of premature beat. On June 29, 1917, 2½ minims of 1 in 1,000 solution of adrenalin chloride were injected into the right median basilic vein, and Chart IV represents the result. This is a normal reaction, and similar to those obtained in Cases I and III. As in the previous cases, this procedure did not produce an attack of tachycardia; neither did the injection of $\frac{1}{30}$ gr. of atropin

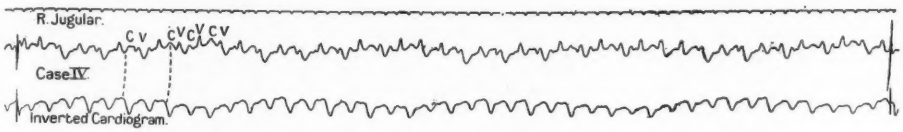


FIG. 5. Case IV. In the jugular tracing there are two waves, C and V.

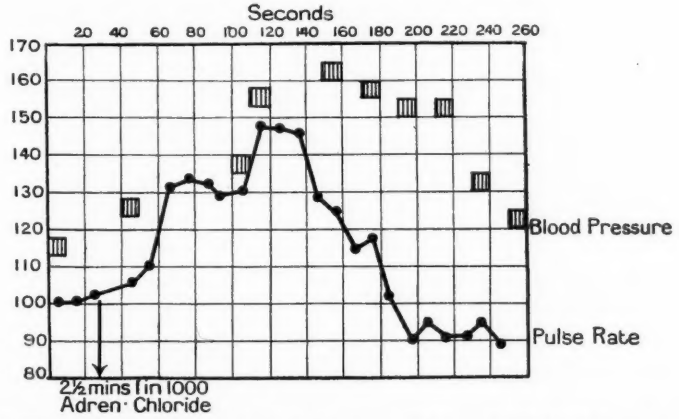


CHART IV. Case IV. Figures on the left indicate pulse-rates and blood pressure.

sulphate cause an abnormal tachycardia, the rate increasing from 60 to 110 and the rhythm remaining normal. The inhalation of amyl nitrite increased the rate from 84 to 108. The inhalation of oxygen diminished the rate of the heart from 94 to 78 and the respiration from 19 to 17; pressure upon the right eyeball reduced the rate of the heart by six beats from 84 to 78.

Case V, aged 34, was admitted on April 22, 1917, with the following history. Six weeks previously he had been seized with an attack of palpitation while up the line. During the following month he had three similar attacks which usually lasted about 2½ hours. The attacks had no apparent relation to exertion, and the patient stated that the eating of hard food would determine an attack. On April 21, 1917, he had two attacks in hospital without obvious cause. He stated that he had been in civil hospitals on three occasions for the same complaint. There was a history of scarlet fever in childhood.

The heart was normal to the ordinary methods of examination. There was no praecordial tenderness, and the rhythm, size, and sounds of the heart were normal.

On the third day after admission to the camp he had an attack of palpitation, and Fig. 6 is a polygraphic tracing taken during the attack; the rate is 260 and there is a single wave in the jugular pulse, the whole of which falls within the period of ventricular systole. No electro-cardiogram was taken in this case. Attacks of paroxysmal tachycardia could not be produced by any form of

exertion whilst he was in the convalescent camp. The injection of 2½ minims of 1 in 1,000 solution of adrenalin chloride produced a normal reaction (Chart V). After the injection of $\frac{1}{30}$ gr. atropin sulphate the heart quickened from 78 to

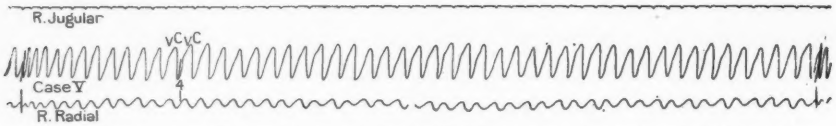


FIG. 6. Case V. There is a single wave in the jugular tracing during an attack of paroxysmal tachycardia.

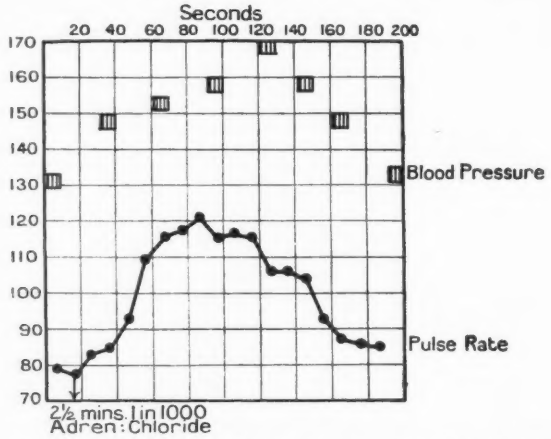


CHART V. Case V. Figures on the left indicate pulse-rates and blood pressure.

109 beats per minute. The attacks of paroxysmal tachycardia in this case were less influenced by exciting causes, such as exertion and emotion, than was the case in the previous patients.

Case VI, aged 40, was admitted on August 1, 1917, with the following history. Fifteen years previously he was seized with an attack of palpitation at a football match, and the attack lasted about 1½ hours. After this occasion he was liable to similar attacks whenever he played football or cricket, and on this account he had to give up the regular playing of these games. As he had a sedentary occupation as a clerk, he could escape attacks of tachycardia by the

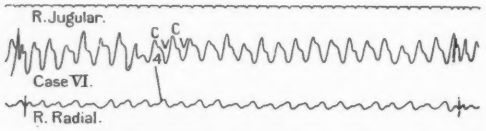


FIG. 7. Case VI. Attack of paroxysmal tachycardia. In the jugular tracing there is a single wave, sometimes bifid.

avoidance of excessive exertion. Since enlistment the attacks had been more frequent, and especially since coming to France, where he was subjected to excitement as well as increased effort. He had been in France for eight months, and during the first fourteen days in the line he had two attacks, and on this account was sent to the Base as a case of shell-shock. Six weeks later he rejoined

his battalion, and as the attacks became frequent, due as he thought to the effects of heavy shelling, he was sent to work on the roads. He managed this work all right until one day he was shelled and he had an attack. This led to his being sent to the Base and to the convalescent camp. On examination the heart was apparently normal; there was no tenderness of the chest-wall, and the size and sounds of the heart were normal. The rate at rest was 60. On August 17, 1917, an attack came on while playing on the football field, and the polygraphic tracing shown in Fig. 7 was taken. The rate is approximately 183. There is a single wave in the jugular tracing and the whole of the wave falls within the period of ventricular systole. No opportunity offered of taking an electro-cardiogram in this patient during an attack. An electro-cardiogram taken in a non-paroxysmal period shows normal P, R, S, T complexes. No further observations were made on this patient.

Discussion.

Six cases of 'paroxysmal tachycardia' in soldiers in France have been described, and the observations which could be made upon them under conditions such as exist in a convalescent camp have been briefly noted.

A study of the histories makes it clear that three of the patients had suffered from attacks of paroxysmal tachycardia before enlistment (Cases I, IV, and VI). In no case was there any evidence of valvular disease of the heart, nor could any infection be traced as the cause of any pathological change in the heart except in Case I: in this case diphtheria had undoubtedly caused a pathological change in the heart muscle which brought about the liability to attacks of paroxysmal tachycardia. In four of the cases attacks could be readily induced by comparatively slight exertion, and it is noteworthy how little general embarrassment the attacks caused.

In view of the fact that there was no gross valvular or muscular disease of the heart, it appeared possible that the attacks might be easily induced by stimulation or depression of the controlling nerves of the heart. Prompted by this consideration, the inhibitory action of the vagus was removed by the injection of atropin sulphate and the sympathetic nerve was stimulated by the injection of adrenalin chloride. In no case did these methods of altering the nervous control of the heart bring about a paroxysmal attack. On each occasion the response was such as is known to occur normally. Nor did alterations in pressure or in the volume of the peripheral circulatory system produce attacks: thus the response to inhalations of amyl nitrite was perfectly normal.

Endeavours were made to increase the venous filling of the right side of the heart by pressure on the abdomen and alterations in posture. On one occasion in Case I a momentary stoppage of the paroxysm seemed to be caused by firm pressure on the abdomen. Two of the patients had discovered that flexion of the thighs upon the abdomen with the head downwards, together with a squeezing of the abdomen by the thighs, would on occasions bring a paroxysm to an end. Inhalations of oxygen and carbon dioxide merely caused slight alterations in pulse-rate.

It was possible to obtain polygraphic records of the six cases, and in Case I the termination of an attack was recorded. The six venous pulses have very similar characteristics: in each there are either one or two waves which fall within the period of ventricular systole, and in none can a separate A wave, evidence of auricular contraction, be detected.

It was hoped that galvanometric records would help the elucidation of the focus of origin of the tachycardia. The R, S, T complexes in Plate 7 have the form associated with premature beats arising in the ventricular musculature. The complexes in Plate 5 suggests this origin also.

A consideration of the venous pulses and the electro-cardiographic records suggests that we are dealing with tachycardias of ventricular origin. What is the state of the auricles during the paroxysm? First, there may be a retrograde stimulation of the auricle from the ventricle: in this case in the venous pulse there is an A wave buried in the V wave, and in the electro-cardiograms a P wave is buried in the T wave.

A second suggestion would be that the auricles are in a condition of fibrillation and that the ventricles are responding regularly to an initiating focus in their own musculature. That the origin of the paroxysm is in the ventricular musculature is supported by the appearance of frequent extra-systoles in Case III during the non-paroxysmal periods.

Summary.

1. Six cases of paroxysmal tachycardia have been described whose pacemaker lies in the ventricular musculature.

2. Attacks of paroxysmal tachycardia were caused at will by exertion in four cases.

3. Stimulation of the peripheral sympathetic system and stimulation and depression of the vagus did not produce attacks of paroxysmal tachycardia.

4. The effects of the inhalation of amyl nitrite, oxygen, and carbon dioxide were recorded.

5. In no case was there any evidence of valvular disease or gross pathological changes in the heart muscle.

I desire to express my gratitude to Major Campbell, D.S.O., R.A.M.C., for permission to publish an account of the above patients, who were inmates of the convalescent camp under his command.

I am obliged to Capt. Marris, R.A.M.C., for the observations on the effects of the inhalation of oxygen and carbon dioxide, and to Major Hay, R.A.M.C., T.F., for discussing the problems suggested by these cases.

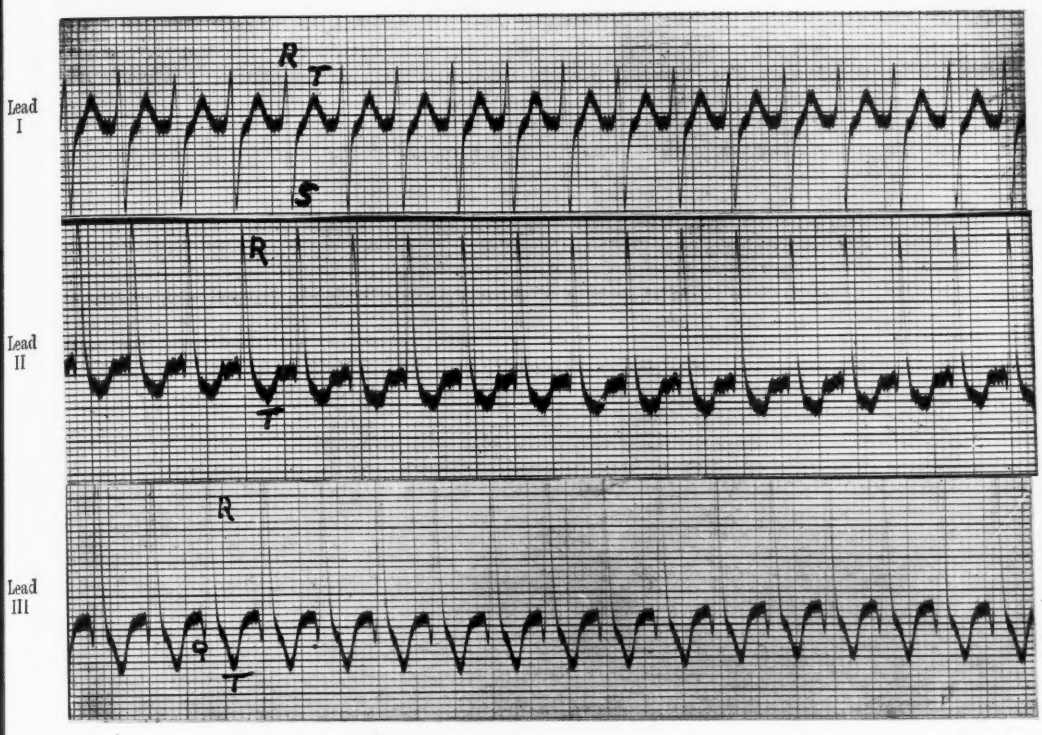


Plate 5. Case I. All three leads show R, S, T (ventricular) complexes

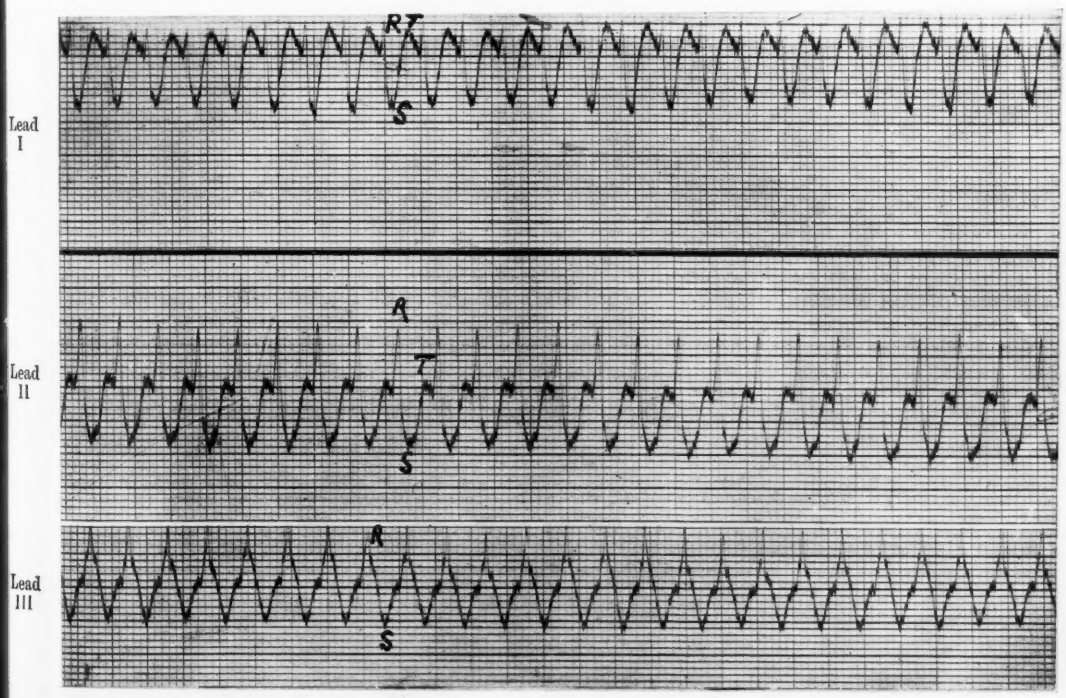


Plate 6. Case III. In each lead there are R and S waves; T appears in leads I and II, but not in lead III

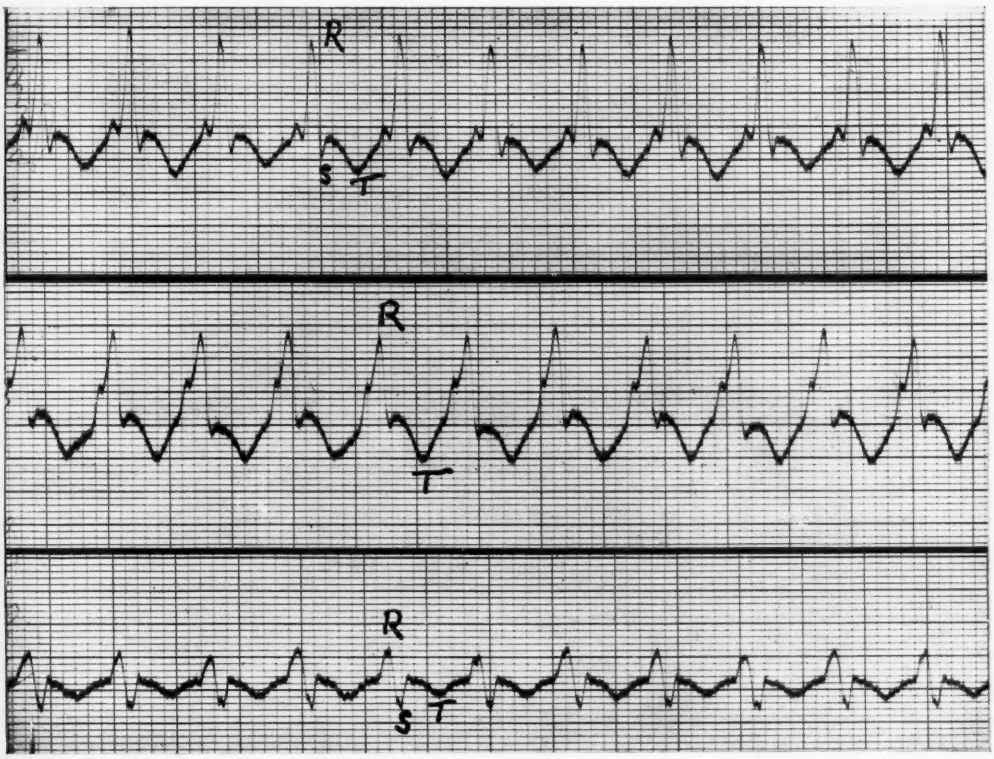


Plate 7. Case IV. R, S, T complexes are seen in each lead

CRITICAL REVIEW

ABSCESS OF THE BRAIN

By W. B. WARRINGTON

With Plate 8

Historical.

The earlier pathologists gradually differentiated the purulent from the non-purulent encephalitis. Then came the recognition of the etiological factors in the causation of abscess of the brain by Toynbee, 1855, in England, and Biermer, 1867, in Germany.

A knowledge of the peculiar symptoms and the diagnosis followed the pioneer work of Wernicke on aphasia. Amongst the earliest attempts to deal with abscess by surgical treatment were those of Barker, Horsley, and Ballance. The classical work of Macewen was published in 1893 and gave an immense impetus to the study of this subject.

Oppenheim's and Cassirer's monograph (1909) gives a full record of the literature of the subject. Of recent years attention has been largely directed to the study of the labyrinth and its rôle in the pathology of the suppurative diseases of the brain, and to the variations in the character of the cerebro-spinal fluid.

Definition. Abscess of the brain is a suppurative encephalitis, and is due to the activity of pus-forming organisms. It is often complicated by septic inflammation of the meninges and of the walls of the veins and venous sinuses, leading to thrombosis of the contained blood.

Etiology.

The infecting organisms obtain access to the cranial cavity in several ways:—

1. *Most commonly from pus foci in the neighbourhood of the brain.*

(*a*) Infection through injury of the skull.

In Gowers's collection of 241 cases of brain abscess, 24 per cent. were due to injury. In recent years the proportion is probably less, owing to the more adequate treatment which wounds of the head have received. Thus of fifty-

four records of abscess recently collected, in only three was the origin traumatic. Macewen makes the following statement: punctured wounds, if penetrating the bone, are particularly dangerous, since they may be overlooked.

Infective thrombosis arises in the diploic vessels and the infection is carried by the perivascular channels to the brain or meninges.

Compound fractures are much less dangerous, since easy egress for the infective material is afforded.

Infection may reach the brain or meninges from an injury without a fracture, if the outer table of the bone has been exposed. An extra-dural abscess may thus result. Injuries may also lead to infective necrosis of the skull, followed by extra-dural or cerebral abscess. Whilst injuries to the flat bones of the skull account for the majority of traumatic abscesses, infection may also

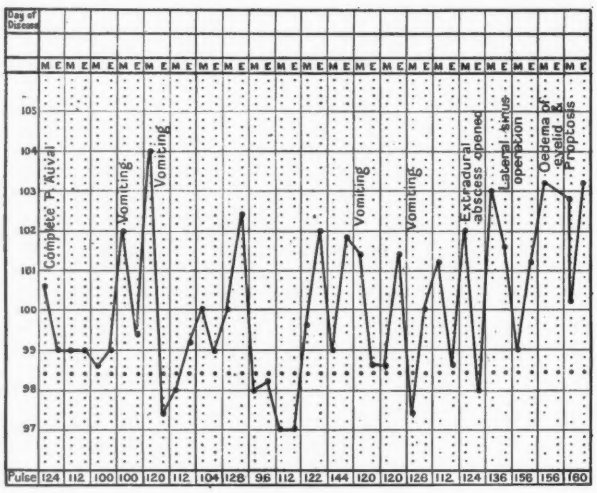


FIG. 1. S. C. Otitic extra-dural abscess; lateral sinus thrombosis; cavernous sinus thrombosis; septicaemia; death. (*Care of Mr. Malcolm Stockdale.*)

follow fracture of the base, the organisms obtaining access through the air-containing cavities of the ear and nose.

(*b*) In a larger number of cases, abscess results from carious processes in the bones of the skull, due to the purulent infections of the mucous membranes lining the cavities in the temporal bone or accessory nasal sinuses.

Owing to the frequency with which the antro-tympanic chambers are infected by micro-organisms from the oral cavity via the Eustachian tubes, abscess of the brain of otitic origin is, nowadays, the most common form met with. Probably half or more of all brain abscesses are otitic.

Rhinogenic abscesses occur much less frequently, but they are well known and follow either suppurative disease of the maxillary sinus, the frontal and sphenoidal sinus, or the ethmoid cells. 120 cases of frontal sinus suppura-

tion, collected by Engelmann, were in five instances complicated by brain abscess.

(*c*) Tubercle, syphilis, and even growths of the bone of the skull may lead to purulent encephalitis.

(*d*) Any suppurative process of the scalp or face, such as carbuncle, erysipelas, or orbital inflammation, may infect the brain or meninges.

2. The second important etiological factor is the infection of the brain via the blood-stream from some distant site of suppuration, leading to the metastatic or haematogenous brain abscess. The most common origin is septic disease of the lungs, especially bronchiectasis, rarely pericarditis, infective endocarditis, liver abscess, dysentery, or disease of the female pelvic organs. Purulent infections in the joints, bones, and skin may also cause metastatic brain abscess.

Shorstein in 3,700 autopsies at the Brompton Hospital, and 10,000 autopsies at the London Hospital, found nineteen cases of cerebral abscesses associated with pulmonary disease, and of these in fourteen the primary lesion was bronchiectasis, in three empyema, in one abscess of the lung, and in one empyema and pneumonia.

Of fifty-eight cases collected by Clayton, the associated pulmonary lesion was in nineteen bronchiectasis, in nine purulent bronchitis, in ten empyema, in seven gangrene, in five tubercle, in three abscess of the lung, in two pneumonia, and in two bullet wounds.

3. Pyaemic abscesses may follow a general infection of the blood from a septic focus; they are not so common, and it is important to remember that pyaemic abscesses of the brain may be of otitic origin.

4. In rare cases, abscess of the brain is found unassociated with any other site of pus formation. Thus the organisms of influenza, typhoid fever, pneumonia, and cerebro-spinal meningitis have been found in the pus of abscesses of the brain, no other lesion being discovered. Whilst in some instances the brain lesion has followed on the symptoms of the general infection, in other cases such symptoms were absent, and we are forced to believe that rarely pus-forming organisms may obtain primary direct access to the brain, causing purulent encephalitis.

The micro-organisms are numerous. Those most commonly met with are the Staphylococcus aureus and citreus, Streptococcus pyogenes, and Fränkel's pneumococcus. Less common are the B. pyocyaneus and B. pyogenes foetidus. Specific micro-organisms, as Pfeiffer's influenza bacillus and the B. typhosus, B. coli, Streptococcus erysipelatis, and the gonococcus, have been found. Many forms of leptothrix, saprophytic, and anaerobic Gram-negative organisms are also often present. The anaerobic bacteria, chiefly from the buccal cavity, are harmless saprophytes, but they may attain pathogenic attributes.

The tubercle bacillus has been frequently found, usually as a mixed infection following tuberculosis of the temporal bone, sometimes from the

softening into an abscess of the solitary tuberculoma, and in rare cases in pure culture of metastatic origin. The actinomycosis has been discovered as a metastasis from affected ribs and from the temporal bone. Oidium albicans is said to have made its way through the pharynx.

The nature and the virulence of the organisms causing pyogenic disease are important in determining the results and appearance of the resulting inflammation.

General Pathogenesis.

Of *intracranial suppuration following traumatism or disease of the bone* certain general statements may be made. Since the intracranial structures are in intimate relationship, inflammation of one of these readily spreads to another. The inflammation may be mild and localized to the outer side of the dura mater, forming a pachymeningitis externa, with possibly an extra-dural abscess. From thence it may spread to the inner surface of this membrane, to which the pia mater may become adherent, the adhesions preventing a general infection, or the inflammatory products may soften and a subdural abscess result. Infection may spread from here and acute leptomeningitis arise; this lesion will also follow if the infection penetrates the dura mater before inflammatory soldering has occurred.

Acute leptomeningitis or abscess may, however, form independently of a visible tract of inflammation, the organism being conveyed by direct vascular connexions. According to Macewen, this is either by an infective thrombosis spreading through the veins into the pia mater or brain, or by a reversal of the blood-stream carrying portions of an infected thrombus inwards. This may occur in the thrombosed veins of the skull on account of the absence of valves, or again the perivascular sheaths of arteries may be infected, local arteritis and thrombosis resulting, and the infected thrombi carried to a distant part of the brain.

Traumatic abscesses may be either acute or chronic. The acute form follows at once upon an injury, the infection causing either a diffuse suppurative leptomeningitis or a focus of suppuration within the cortical substance of the brain—the cortical brain abscess. Such an abscess is situated in the immediate vicinity of the wound, which is obviously septic, or pus may be seen issuing.

A chronic abscess may result if the virulence of the microbe be low and the resistance of the patient high. In such a case the septic focus may be walled up by the formation of the pyogenic membrane, but softening may take place from acute exacerbation of reinfections.

Chronic abscesses may thus exist for many years; they may be found directly under the site of the bony lesion, or deep in the corresponding part of the hemisphere. In rare instances when the skull has been fractured by contrecoup the abscess may be at a distant site; thus a blow on the occipital region has caused abscess of the frontal lobe.

Head injuries and their treatment have received much attention during the

War. The writer has no first-hand experience in this matter and refers the reader to current medical journals. Very few instances of chronic abscess have occurred in the First Western Command. Those which the writer has seen have attracted notice many months after the original lesion, and their formation has followed in accordance with the principles stated. The cases of injury resulting in local forms of infection of the meninges and in hernia of the brain strongly support the view of those who advocate conversation surgery; they show the immense barrier to infection provided by an intact dura mater and indicate that the brain matter itself can deal with some forms of infection.

Inflammation of the middle ear as a cause of intracranial suppuration, chronic purulent otitis media, is the infection which most frequently leads to intracranial complications, and especially when this is associated with cholesteatoma. As a rule the otitis has existed for a long time, even for many years. An otitis is most likely to cause brain disease during periods of acute reinfection, or if free egress of the pus be prevented by polypoid growth or granulomata. In children the otitis may be caused by infection of the tympanic cavity following the common specific fevers, and is sometimes associated with tuberculosis of the petrous bone.

An intimate knowledge of the relationship of this cavity is necessary to understand the paths of encephalic infection, and for these the reader is referred to special treatises.

The mucous membrane lining of the cavity extends to inaccessible recesses. When it becomes inflamed much depends on the duration and the virulence of the infection. If the infection be acute and not too severe the mucous membrane may recover and the underlying bone remain healthy, but in chronic processes pronounced changes occur in the mucous membrane, and the nutrition of the bone is affected and may ultimately lead to caries, necrosis, and perforation. The infection is either directly conveyed to contiguous structures, or by vascular propagation in the manner already described. It is important to remember, however, that an acute otitis may lead to brain abscess when the infection is a virulent one. Heimann gives the proportion of abscesses following respectively chronic and acute otitis as 80–20, Neumann as 88–12. Okada says that cerebellar abscesses are especially likely to result from acute otitis. Although the disease within the tympanum usually destroys the tympanic membrane, yet disease may exist although this membrane is intact, and brain abscess may occur when the otitis has been cured.

Since in children the several parts of the temporal bone are not firmly intact there is freer egress for inflammatory products than in adults, the walls of the tympanum are less liable to become carious, and abscess of the brain is relatively less frequent than in adults. On the other hand, the vascular communications between the bone and intracranial structures are greater, and hence meningitis is frequent. Cheatle has described, under the description of infantile types of temporal bone, a condition of absence of the cells of the mastoid which increases the risk of intracranial infection. The relative fre-

quency with which the different parts of the temporal bone are attacked by caries and necrosis is given by Macewen as follows: (1) mastoid region; (2) roof of tympanum and antrum; (3) sigmoid grove; (4) posterior wall of the external auditory canal; (5) the tympanic floor with the posterior wall of the carotid canal; (6) the petrous portion, including the structures constituting the middle ear. Tylor, from his recent investigations, gives: (1) the mastoid region; (2) the roof and posterior wall of the mastoid antrum; (3) the inner tympanic and antral wall leading to labyrinthine fistulae.

In children, especially in tuberculous infection, a common site of caries is the neighbourhood of the facial canal in the tympanum. It is from these sites that infections spread to the posterior or middle fossa of the skull, and the infections that may result are: (1) brain abscess; (2) extra-dural abscess and subdural abscess; (3) sinus thrombosis; (4) purulent meningitis; (5) serous meningitis or ependymitis and inflammatory oedema of the brain.

Special Pathogenesis.

Otitic brain abscess. For practical purposes otitic abscess occurs either in the temporo-sphenoidal lobe or the cerebellum. Of 645 cases collected by Heimann, 395 were in the temporo-sphenoidal lobe, 186 in the cerebellum; a proportion of about 2 to 1. It seems certain that abscess in the hemisphere is more frequent than abscess in the cerebellum. In a few cases otitic abscesses have been found in the occipital or frontal lobe, and as curiosities they have been recorded as occurring in the cerebral convolutions, in the optic thalamus and pons.

When due to direct invasion, the common method of origin, they are necessarily on the same side and are usually single. Multiple abscesses, however, occur sufficiently often to be of surgical importance. There may be two or more abscesses in the same region of the brain, and abscesses in both the hemisphere and cerebellum.

Otitic abscesses are in nearly half the cases associated with other forms of intracranial lesions, as exhibited in the following table from Heimann. Out of 645 cases of brain abscess in 303 there were complications.

Complications in Otitic Abscesses of the Brain.

	Recovery.		Fatal.	
	Acute.	Chronic.	Acute.	Chronic.
Sinus thrombosis	1	5	4	47
,, ,, and meningitis	—	1	3	18
,, ,, and extra-dural abscess	2	3	—	10
Extra-dural abscess	5	19	6	14
,, ,, and meningitis	—	—	1	8
Pachymeningitis	3	8	4	14
Meningitis	—	2	20	87
Encephalomeningitis	—	1	2	12
Pneumonia	—	—	—	2
Rupture into internal carotid	—	—	—	1
	11	39	40	213

In most instances the path of infection can be traced from the carious bone and diseased mucous membrane to the dura mater, and from thence to the brain. The temporo-sphenoidal abscess arises from infection through the tegmen tympani and in children through the patent squamo-petrosal fissure. The path of infection for cerebellar abscess is through the mastoid process with or without infection of the lateral sinus, or through the labyrinth. The frequency with which the infection spreads to the middle fossa from the tegmen tympani is due to the thinness of this bony wall, which may also show dehiscences; similarly, the bony plate which separates the cells of the mastoid from the fossa sigmoidea may be even thinner; hence the majority of cerebellar abscesses are in direct contact with the sinus transversus.

The importance of infection of the labyrinth leading to cerebellar abscess is in recent years becoming increasingly recognized; according to Brühl (1913) the common path of infection is through either the foramen ovale or foramen rotundum, and more rarely through dehiscences in the thin bony wall of the promontory of the external semicircular canal. Neumann believes that whilst in acute otitis the labyrinth plays no rôle in the development of intracranial affection, in chronic disease, on the other hand, labyrinthine suppuration is the most important source of infection leading to cerebellar abscess.

Koch states that the two chief sites from which the cerebellum becomes infected are the sulcus of the sinus sigmoideus and the labyrinth.

The infection passes from the labyrinth to the cerebellum via the internal auditory meatus along the seventh and eighth nerves, and leads to either diffuse meningitis, pachymeningitis, or cerebellar abscess.

The great frequency with which the direct path of infection can be traced is shown by Körner's statistics. In 42 per cent. of the cases observed by him a fistulous tract was found connecting the abscess with the primary disease in the temporal bone. In 15 per cent. there was a tract through the brain substance between the abscess and dura, and in 17 per cent. the intermediate brain substance was softened and discoloured.

Occasionally the direct path is through the lateral sinus, and in one case under the care of Mr. Hugh E. Jones the infection had spread by direct continuity along the sinus to the temporo-sphenoidal lobe of the opposite side.

In the remaining instances, where no direct path can be found, the infection takes place through vascular channels and distant abscesses form. When situated in the opposite half of the brain the source of infection is by metastasis or pyaemia.

Lateral sinus thrombosis. Tylor found this lesion in 20·5 per cent. of the cerebral complications of infective middle ear disease, and in about 30 per cent. it was associated with an extra-dural abscess. It was usually caused by direct extension from the mastoid and antrum cells; occasionally the bone was not affected, and infection was probably conveyed by venous tributaries to the lateral sinus. The thrombosis is frequently due to direct extension from an extra-dural (perisinus) abscess. The thrombotic process may also start from

a vein draining into the superior petrosal sinus and from thence to the lateral sinus. Another site of infection, the rôle of which is not yet definitely ascertained, is via the aquaeductus vestibuli; this contains the ductus endolymphaticus, widening at its termination to the saccus. By the ductus the perilymph of the vestibule is in intimate relationship with the dura mater of the lateral sinus, and when infected an empyema of the saccus may develop.

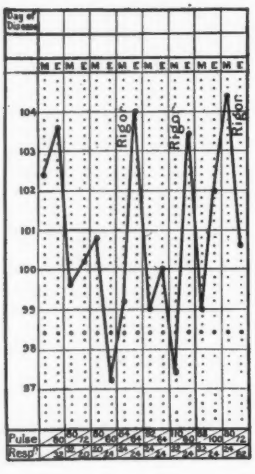


FIG. 2. J. W., aged 29. Lateral sinus thrombosis with cerebellar abscess; note relatively slow pulse; operation; death.

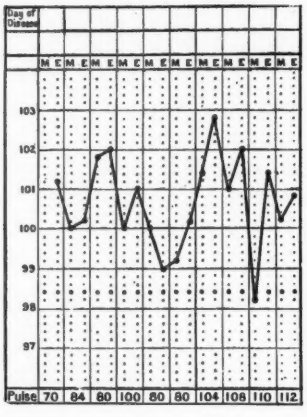


FIG. 3. Case of tuberculous meningitis simulating left temporo-sphenoidal abscess. E. L., aged 13. Double otorrhoea since 7; admitted with r. offensive otorrhoea; left membrane scarred and calcareous; no discharge; patient mentally dull with paraphasia; four days later r. hemiplegia developed; abdomen slightly retracted and slight Kernig's sign. Lumbar puncture: marked lymphocytosis. P.-m.: tuberculous meningitis, especially along r. Sylvian fissure.

Extra-dural abscess. The neighbourhood of the sulcus lateralis is the most common situation in which an extra-dural abscess forms from infection spreading through the posterior walls of the antrum or posterior cells. It may be accompanied by thrombosis of the lateral sinus, or by a cerebellar abscess. Extra-dural abscesses are also found in the middle fossa following disease of the roof of the tympanum.

Intra- or subdural abscess. This is localized leptomeningitis; it produces the ulceration of the brain described by Macewen and its pathogenesis is the same as abscess. It is sometimes found in connexion with an extra-dural abscess.

Purulent leptomeningitis, either localized to the base or generalized, may arise from any of the lesions mentioned, or there may be direct extension from the tegmen, the mastoid cells, antrum, or labyrinth.

Serous Meningitis and Inflammatory Oedema of the Substance of the Brain.

Brain disease from disease of the nasal and accessory cavities. There is always disease of the bones. In abscess resulting from frontal sinus disease a perforation can usually be found in the posterior wall of the sinus. An extra-dural abscess may form. Spontaneous dehiscences have been found. When no direct path can be demonstrated the infection is carried by infected veins from the ethmoid cells or by lymphatics. Septic infection of the ethmoid cells most commonly leads to meningitis, and in fact the meninges are not infrequently infected by operation. Cavernous sinus thrombosis is very rare. Infection may also be conveyed by the olfactory and optic nerves. The frontal lobe is the region always invaded.

Brain abscesses from metastasis or pyaemia. These result from emboli breaking away from septic thrombi formed at the site of the primary disease, and hence they are usually multiple.

Morbid Anatomy.

Abscesses occur in any part of the brain and the site depends upon their causation. The traumatic abscesses are at the site of the injury, and are either situated in the cortex, when they are acute and of recent formation, or more deeply placed when they are of slow evolution—the traumatic late abscess. The otitic temporo-sphenoidal lobe is most commonly found in the third convolution just at the border and convexity of the base of the brain. This spot is in the most direct connexion with the roof of the tympanum. In rarer instances the abscess is more anterior and even at the apex of the lobe. Usually the abscess is situated some little distance from the surface or is deep-lying. The smaller the abscess the more superficial it is (Körner). Occasionally the abscess is so large as to invade the occipital lobe, and it may in growing invade the neighbourhood of the basal ganglia and internal capsule. The fistulous tract leading to the site of infection can often be found. Cerebellar abscesses most commonly lie in immediate relationship to the fossa sigmoideus of the sulcus transversus and are in the outer and anterior region of the cerebellum. If the infection is from the labyrinth the abscess is situated in a more median position. Traumatic and otitic abscesses are usually single; according to Macewen 93 per cent. in traumatic and 87 per cent. in those of otitic origin.

Metastatic abscesses are somewhat more often multiple than single (thirteen out of twenty-two, Martius). They are nearly always in the hemisphere, most commonly in the region of the cerebral ganglia, or near the cortex, but they have been found in the cerebellum, pons, or medulla. In size abscesses vary greatly; if of pyaemic or embolic origin they are usually small and may be extremely

small, though by coalescence a large mass of the brain may be destroyed. They may contain from a few drops to several ounces of pus. The largest abscesses are to be found in the temporo-sphenoidal lobe.

A purulent encephalitis consists of pus cells and nervous tissues in varying stages of disintegration and necrosis. Microscopically, at its most external part, débris of nervous tissue can be seen infiltrated with leucocytes. The wall, at first irregular in outline and thin and delicate, gradually increases in thickness.

Internal to this stratum, leucocytes are found in larger numbers and the products of nervous degeneration are more advanced, whilst in the centre little remains but amorphous granular deposits and nuclear remnants of nerve cells and leucocytes. As the age of the abscess increases the outer layer forms a definite capsule which may become very thick, stratified, and even calcareous.

The traumatic late abscesses and the chronic otitic abscess are usually encapsulated. Otitic abscesses of recent origin, the cortical recent traumatic abscess, all pyaemic and most metastatic abscesses are devoid of a capsule. These free abscesses may be defined from the surrounding brain tissue by a soft necrotic margin. A well-formed membrane may perhaps be present in abscesses of five to six weeks' duration.

Some authors (Neumann and Gohn) assert that capsule formation is due to the activity of the Gram-positive diplococci, whilst anaerobes give rise to ill-defined abscesses which refuse to heal and contain thin highly stinking pus. The contents of the abscess consist of pus, often greenish in colour and acid in reaction ; sometimes it resembles curds and whey, or is coffee coloured, creamy, red, or grey. Bacteria like those of the primary infection are present and the odour may be foetid.

The growth of the encapsulated abscess takes place either by new formation of pus cells from the membrane, or by a melting down of the central parts of its contents, and through the fresh reinfections from the primary site. The tissue outside the abscess is often swollen and oedematous, and this associated state has an important rôle in the symptomatology. The complications of brain abscesses have been mentioned and their frequency shown in Heimann's table.

Cerebellar abscesses are more frequently complicated by associated lesions than temporo-sphenoidal abscesses, one reason for this being the greater frequency of sinus thrombosis.

Symptomatology.

The symptoms presented by abscess in the brain are very variable, the clinical history being largely influenced by its causation and rate of formation and the presence of the other intracranial lesions.

Abscess may be considered as acute or chronic.

An acute abscess may run its course in ten to twenty days, or death may occur in a shorter period from such a complication as meningitis.

Metastatic abscesses, pyaemic abscesses, and the cortical traumatic abscess are acute, and also a smaller portion of abscesses of otitic origin.

The symptoms may be entirely masked by those of the primary disease, or if arising from otitis may be continuous with those of the primary infection. On the other hand, in chronic abscesses, i. e. most otitic abscesses and late traumatic abscesses, the symptoms of the initial period of formation subside and are followed by a latency in clinical manifestations, a period which may last for years. This latent period is interrupted by symptoms which are characteristic of abscess.

It is a mistake to distinguish sharply between acute and chronic abscess; they merge into one another and a chronic abscess is probably often reinfected, i. e. undergoes a second acute inflammatory process. Hence it is customary for descriptive purposes to consider the symptoms of abscesses as those of (1) the initial stage; (2) the latent period; (3) the manifest illness; (4) the terminal stage.

In *the initial stage*, the symptoms have little that is characteristic; they consist of pain in the head, vomiting, fever, and usually an accelerated pulse-rate. Sometimes local signs are present, such as rigidity of the neck and partial convulsions. The only additional remark called for concerning the initial stage symptoms is that the non-disappearance of inflammatory symptoms after the primary focus has been adequately dealt with should arouse suspicion that intracranial mischief may be present, and the symptoms should not too readily be considered to be due to either a septicaemia or a transitory sapraemia.

The latent period. During the latent period many persons continue their ordinary occupation without obtrusive signs of ill health. It is likely, however, that temporary headaches, mental changes, giddiness, and other cerebral signs are experienced during this period. Should patients complain of such obscure symptoms and a possible site of infection be discovered the possibility of intracranial suppuration must be borne in mind. The temperature is usually normal, but there may be attacks of intermittent fever.

The manifest stage. Symptoms of the manifest stage are: (1) general constitutional signs; (2) general signs of brain disease; (3) localizing signs. Obviously the otitic, traumatic, and metastatic abscess have many features peculiar to themselves, but much of the clinical history is common to abscess of the brain from whatever source it may arise; these common symptoms will first be indicated, and afterwards the distinguishing features mentioned which are dependent upon the etiology.

1. *General constitutional symptoms.* The temperature is variable. In the earlier period rigors may occur. Macewen says that this is one of the most constant early symptoms. There may be either a mere feeling of cold or pronounced rigor. Repeated rigors may also occur, though rarely in an uncomplicated case. Even in the absence of rigors the temperature is usually slightly over normal. Soon after this initiatory fever the temperature becomes normal or subnormal, though it may from time to time rise slightly above the normal.

The normal or subnormal temperature is probably almost the rule in *uncomplicated* cases. Neumann out of 146 cases of cerebellar abscess found 61 with a febrile course; 85 were afebrile. Nothnagel considered the cause of the low temperature to be a remote effect of the abscess on the heat-regulating centres. Fever is less likely to occur in an encapsulated abscess. Its presence is an indication to search for activity in the primary focus, to suspect sinus thrombosis or a form of meningitis.

Leutert traces it to a transitory serous meningitis; Hoffmann to a circumscribed purulent meningitis. Other constant constitutional symptoms are marked anorexia, gastric disturbance, and constipation with foetor of the breath and a foul tongue. Prostration is often very marked; the face is sallow, and even of icteric tinge.

2. *General signs of brain disease.* The most important cause of these is the increased intracranial pressure. Pain in the head is early and constant, and it is usually very severe and may be subject to terrible exacerbations.

Any cause that raises the blood pressure in the brain increases the pain, such as coughing; or drugs, such as alcohol or coffee. It is increased by movement of the head. It may be localized to some extent to the site of the abscess; thus in otitic cases the pain is often in the ear, extending to the temporal area and radiating to the frontal and occipital region. The region of the pain may be tender to pressure or percussion. Vomiting is very rarely absent; it is unaccompanied by nausea and tends to be more frequent with the exacerbations of the pain. Giddiness is frequent.

Disturbance of the sensorium and of the mind is an important symptom. The mind is dulled; the cerebration is slow; questions will be answered correctly and after a pause; later on answers become merely monosyllabic, attention cannot be sustained, and the patient easily sinks into a dozing condition, and becomes more and more difficult to arouse.

The pain becomes less intense. Restlessness, delirium, and excitement are sometimes present, especially in the early stage, and even furious mania alternating with coma has been seen. The pulse is significant, characteristically it is slow and full, sinking to 60, 50, or even 30 per minute.

The slowness of the pulse may sometimes be out of proportion to the degree of cerebral compression, and may then be attributed to the toxic oedema of the brain tissue. The relative slowness of the pulse is often a feature also when the temperature is raised, and a quickened pulse-rate may be due to some complication or to tension in a primary focus. Many other causes of cerebral compression cause slow pulse, and though the fact that the pulse often rises at once after the evacuation of an abscess shows that pressure is a factor in its causation, yet other causes probably operate.

Respiration is slow, especially in cerebellar cases, and may even be of the Cheyne-Stokes character. The sudden and fatal cessation of respiration has frequently been noted.

Optic neuritis is common. According to Schwartze it occurs in 42 per cent.

of brain abscesses. It rarely attains a high degree, though its advance may be observed from day to day. It is more often more marked on one side, but there is no evidence that this is on the side of the abscess. The neuritis may increase for a time even after the evacuation of the abscess, but if recovery occurs it disappears completely and vision is unaffected.

3. *Localizing signs of temporo-sphenoidal abscess.* Small abscesses may cause no local signs, but the great majority of uncomplicated temporo-sphenoidal abscesses cause at least some localizing signs.

Aphasia in left-sided lesions is not uncommon, and some disturbance in the faculty of language is present in more than half the cases.

Oppenheim says the rule is for there to be partial, rarely complete, word deafness, amnesic aphasia, paraphasia, or alexia with or without agraphia and optic aphasia. He writes: 'The characteristic speech defect is sensory aphasia or word deafness, and this is rarely complete and simple. It is usually united with paraphasia and amnesic aphasia. Spontaneous speech may be almost unaffected.'

In many cases the spoken word is only slightly influenced, yet there is an impossibility to utilize the memory of the sound of the word, leading to a more or less marked amnesic aphasia. The patient speaks only a little, he cannot recall many words, and so great may this defect become that he does not speak at all and presents the features of a motor aphasia. The patient will only obey the simplest commands and will constantly repeat the requested movement, i. e. the symptom of perseveration.

The paraphasia is characterized by the inability to use nouns. In attempting to read the patient says nonsense and has no knowledge of the meaning of the written word. Pick and Oppenheim have shown that when abscess lies in the basal, posterior, and deeper lying part of the temporal lobe the auditory and visual centres may be disconnected and there results a partial word deafness, so that words which have no visual content can be understood.

Crossed hemiparesis is an important sign; the face, arm, and leg may be weakened together, or there may be monoplegia of the face and arm, or the leg may be most paralysed. There is rarely complete loss of power. The reflexes show the characteristic change following a pyramidal lesion. Macewen considers that, if the face is first and chiefly affected, the arm in a lesser degree, and the leg slightly, whilst sensation is intact, the lesion is caused by pressure upon the cortex; if, on the contrary, the order of paralysis is reversed, and especially if there is sensory loss, the lesion is influencing the region of the capsula interna.

Oppenheim believes, however, that the internal capsule is the usual site affected in the hemiplegia of temporal lobe abscesses.

Oculomotor paresis. A partial homolateral paralysis of the third nerve is often present and is an important diagnostic sign. It is rarely complete. Ptosis or a dilated immobile pupil is the most common sign, and it is important that the condition may be only temporary. Macewen lays great stress upon the simultaneous contralateral hemiparesis and homolateral oculomotor paresis in

the diagnosis. Narrowing of the pupil may also have significance, though the pupil alone may be affected by lesions elsewhere than in the temporal lobe. Paresis of the abducens is rare.

Hemianopsia has been met with as an indirect localizing sign. It is due either to a deeply seated abscess or to the spreading of inflammatory oedema or softening. Deafness on the opposite side may be significant.

Local signs of abscess in the motor region. Traumatic and metastatic abscesses frequently invade the cortex or the underlying white matter and directly or indirectly evoke well-marked signs. The acute traumatic abscess is essentially a cortical abscess. The characteristic signs are the Jacksonian epilepsy and varying degrees of monoplegia and hemiplegia. In much rarer cases some form of loss of sensation can be discerned; complete asterognosis was observed by Bibrowicz, due to a traumatic abscess of the parietal region.

Local signs of frontal abscess. Abscesses in this region are traumatic, metastatic, or rhinogenic. Unless the abscess presses backwards local signs may not be discovered. Exophthalmos has been noticed on the side of the lesion, and in one case conjugate deviation of the head and eyes towards the opposite side. Certain mental states are held to be characteristic of frontal lobe disease and have been met with in frontal lobe abscess.

Local signs of occipital abscess. Abscesses in this region are traumatic or metastatic in origin. Homonymous hemianopsia is the characteristic symptom. Edwin Bramwell has recorded a case with visual aura and hemichromatopsia. Occipital lobe abscess may by pressure cause cerebellar signs or hemiparesis and convulsions.

Local signs of cerebellar abscess. It is now well known that lesions of the cerebellum give rise to easily recognizable clinical signs. The influence of each lateral lobe is exerted homolaterally, that of the vermis bilaterally. In small abscesses of the cerebellum they may be completely absent, and even in larger ones experience shows that the signs are not usually so frequently found or so pronounced as in cases of tumour.

The symptoms that may arise are: (1) ocular paresis; (2) subjective and objective disorders of the equilibrium; (3) asynergia; (4) atonia and homolateral paresis.

Ocular paresis. The commonest symptom is paresis of the abducens muscles, but its diagnostic value is very small. Deficiency in the power of conjugate movement towards the affected side is of much greater significance, indicating interference with the connexions from the third to the sixth nuclei. Skew deviation of the eyes is highly characteristic; the eye on the affected side tends to be directed upwards and outwards, and that on the opposite side downwards and outwards. Nystagmus is frequently present, and on deviation of the eyes to the affected side. Towards this side the movements are longer in range and more constantly present. Whilst a sense of giddiness may be present in many intracranial conditions, a definite sense of vertigo and of apparent rotation of objects is suggestive of cerebellar lesions. If the patient be in a condition to

attempt to walk the gait is slow, showing the characteristic staggering with a tendency to fall to the side of the lesion. The behaviour of the limbs on the affected side gives important evidence.

Asynergia of the upper limb is shown by the uncertain way in which movements of the limb, directed to some given object, are performed. Thus in the finger to the nose test the hand oscillates around the line of most direct movement. Similar disturbance is shown by the movements of the lower limbs.

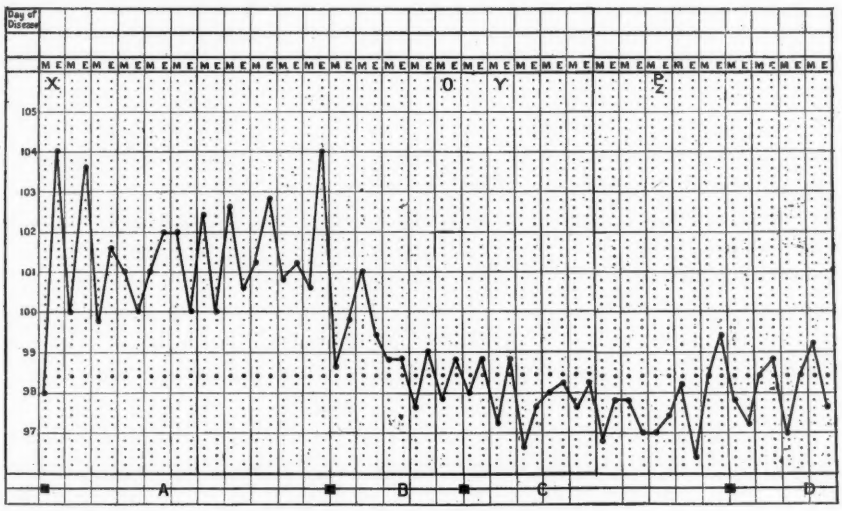


FIG. 4. Left cerebellar abscess. (*After Mr. Wilfred Trotter.*)

Patient aged 25. Discharge from l. ear for 3 months; admitted with tenderness over mastoid; radical operation immediately performed.

(A) Stage 1: symptoms, headache and feeling of illness; average minimum pulse-rate 70 per minute.
(B) Stage 2: headache, feeling of illness, giddiness, drowsiness; average minimum pulse-rate 62.
(C) Stage 3: headache, feeling of illness, giddiness, drowsiness, ocular signs, vomiting.
(D) Stage 4: rapid disappearance of symptoms; average pulse-rate 83·5.
(X) Mastoid operation.
(Y) Cerebellum explored, result negative.
(Z) Cerebellar abscess opened.
(O) First appearance of ocular signs and the onset of vomiting.
(P) Appearance of cerebellar paresis.

The asynergy may also be seen on attempting to perform rapidly alternate pronation and supination of the forearm—dysdiadokokinesia—and also in making the movements of flexion and extension of the elbow and knee joints.

The limbs are characteristically flaccid and atonic; the thigh may even be capable of flexion on the pelvis beyond the right angle. The atonia may be so great as to cause a form of paresis. The reflexes are not characteristically altered, the knee-jerk response may be inconstant and variable, unilateral

alteration is suggestive. Ankle clonus or the extensor plantar reflex are never present.

If this group of signs can be discerned the diagnosis of lesion of the cerebellum is almost certain. It is rare, however, to meet with cases of cerebellar abscess which exhibit a combination of many of these signs; they are most likely to be found in chronic abscesses which have been latent for a long time.

In practice otitic cerebellar abscesses are met with associated with a variety of other intracranial complications and presenting varying clinical pictures. The abscess is rarely uncomplicated, and in the majority of cases one or more of the following lesions are present:—sinus thrombosis, extra-dural abscess, fistula to the external or superior semicircular canals, labyrinthitis or leptomeningitis. In such cases the diagnosis can only be certainly made by observation during and after the complete post-aural operation. Many of these conditions have symptoms common with those of cerebellar disease. Further, they may make the examination of the patient difficult. Acute abscess formation is rarely accompanied by characteristic focal signs, but it is important to notice that Neumann found only one instance of doubtful labyrinthine suppuration in nineteen cases of acute cerebellar abscess; hence the especially masking signs of labyrinthitis do not in acute cases interfere with the diagnosis. On the contrary, in chronic abscess, Neumann states that out of 132 cases labyrinthine suppuration was present in practically 50 per cent.

Dench, in an analysis of 103 recorded cases of cerebellar abscess, found the most prominent and constant symptoms to be:—in 71 headache, rarely localized; in 54 vomiting, often constant; in 30 vertigo; in 17 nystagmus; in 12 stiffness of the neck; in 44 stupor; in 3 Cheyne-Stokes respiration; in 3 cessation of respiration at the operation; in 26 temperature subnormal; and in 5 the temperature high. Neumann gives a précis of some 160 cases. Pain in the head was very constant, and in one case it was so intense as to indicate the correct diagnosis in the absence of other physical signs. Vomiting and vertigo were both frequent. A high temperature was mentioned as present much oftener than a subnormal one; rigors were noted in a number of cases. The characteristic slowing of the pulse was often helpful, but in a great many cases the pulse was raised in frequency. It is in uncomplicated temporo-sphenoidal abscess that the infrequent pulse and low temperature is more commonly found. Of the distinctly focal signs, all of these occurred, but they were often absent and very rarely indeed in classical combination. Vertigo was the most common, and next nystagmus, which in a great majority of the cases was directed towards the side of the lesion. The staggering gait and homolateral weakness were noted in a small number. Palsies of the third cranial nerve were observed in a fair number of cases, but very rarely either abducens paralysis, conjugate palsy, or the peculiar skew deviation. The chief points brought out by a study of Neumann's collection show: (1) the rarity of uncomplicated cerebellar abscesses; (2) the importance of distinction from suppurative labyrinthitis; (3) the rarity with which the

full picture of the sign of cerebellar abscess is found in any one case; (4) the difficulty of the diagnosis and the necessity of forming an opinion *inter operationem*.

Patients may first be seen when semi-comatose or even comatose. The only symptoms available may then be the slowness of the pulse and respiration, subnormal temperature, emaciation, ash-grey pallor of the face, prominent molars and sunken eyes, the presence of optic neuritis, the negative findings of lumbar

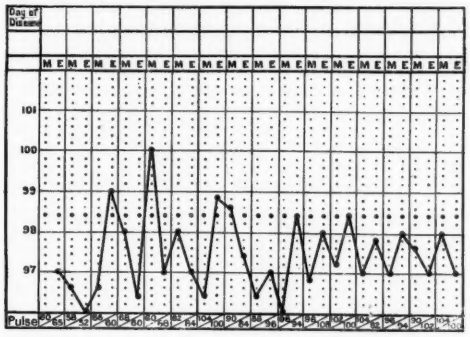


FIG. 5. Uncomplicated r. temporo-sphenoid abscess.

J. T., aged 34. Frontal headache since 14; no history of ear disease; five days after admission l. hemiplegia and double optic neuritis developed.

puncture, and the presence of leucocytosis. If semi-comatose, Macewen has pointed out the significance of rigidity of the masseters, frequent yawning, deficient and jerky articulation. One of his patients before admission had remarkable attacks of unconsciousness, with livid, turgid face, and stertorous breathing. Such seizures have been described by Potts with sudden attacks of vertigo, roaring noises in the head, relaxation of the limbs, and falling with loss of consciousness.

Diagnosis.

The diagnosis depends in the first instance upon a consideration of the etiology, and has to be made from: (1) other intracranial lesions of similar origin, (*a*) suppurative, (*b*) non-suppurative; (2) tumour of the brain; (3) general constitutional disease.

Etiological factor in the diagnosis. In general it is impossible to diagnose abscess of the brain, unless a cause for intracranial suppuration can be discovered. It must be remembered, however, that the late traumatic abscess may exist when all signs and even all recollections of an injury have long passed away; that infective disease of the mastoid may exist without otoscopic changes, and that a metastatic abscess may be the result of an apparently slight and healed superficial phlegmon. In the diagnosis of brain abscess the existence of otitis media, either past or present, is of the utmost importance. Symptoms may only appear years after an aural infection which may have had its inception in ear disease of childhood.

Diagnosis of traumatic abscess. If acute, the wound is unhealthy and septic, or if open, pus may be seen issuing; if closed, the scalp is oedematous, forming Pott's puffy tumour. In compound fracture the base of the wound may lead to yellow, dry, unhealthy looking brain tissue. The signs of localized convexity meningitis are identical with those of cerebral cortical abscess, and a differential diagnosis cannot be made. It is important to note, however, that whereas meningitis may develop very soon after injury, an abscess requires at least 7 to 14 days before the appearance of the symptoms. If at this period headache, vomiting, fever, disturbance of the sensorium appear, and are followed by localizing signs, abscess is to be suspected. General diffuse meningitis must also be considered. Traumatic late abscess is more difficult, since there may be no indication from the state of the scalp. Localizing signs, further, are not so distinct, since the abscess is situated deeply and, more often than not, is in a part of the brain lesion which does not give rise to readily observed symptoms. We have often to rely upon evidence of increased intracranial pressure, preceded by a long period (the latent period) of outbursts of ill health, characterized by headache, psychical depression, vertigo, nausea, perhaps a slow pulse, and variations in the temperature, either in the direction of fever or subnormal temperature.

It is to be borne in mind that syphilis, tuberculosis, actinomycosis, and even new growth of the flat bone of the skull may give rise to underlying abscess of the brain. Certain conditions other than purulent encephalitis may arise as the result of injury to the skull and are to be excluded. These are meningeal haemorrhage, chronic meningo-encephalitis, and acute haemorrhagic encephalitis. Haemorrhagic encephalitis may follow an aseptic wound or simple contusion; whilst most commonly the brain stem is the part affected. Occasionally the symptoms arise from infection of the brain near the site of the injury. This pathological state terminates in death in a few days, or by complete restitution, or leaving a slight residuum of local signs.

Otitic abscesses. It is only when the symptoms point to brain disease on the same side as the ear disease that diagnostic significance can be attached to the combination. The examination of the parts displayed by the surgeon during the performance of the radical mastoid operation is of the utmost importance.

Otitic abscess may be symptomless; according to Neumann 9·4 per cent. of abscesses of the cerebellum do not cause symptoms. The presence of choleasteatomatous growths favours the coexistence of an abscess.

Practically speaking all otitic abscesses, except as the result of metastasis or pyaemia, are either in the cerebellum or temporo-sphenoidal lobe, but other parts of the brain may be influenced so as to cause 'distant' signs, or may be affected by complications such as circumscribed or general meningitis. The diagnosis from tubercle may be difficult. Tuberculosis of the petrous bone may cause either tuberculoma of the brain or tuberculous meningitis, or these may be combined. The tuberculoma is often multiple and the symptoms may not be consistent with the known sites of abscess, yet tuberculoma notoriously affects the cerebellum and may even undergo abscess transformation. Tuberculoma runs a more

gradual course than abscess, and examination of the cerebro-spinal fluid may reveal the presence and nature of any meningitis. But, especially in children, a certain diagnosis may be wellnigh impossible.

Nasal abscess. This is homolateral in the frontal lobe, usually chronic; but acute abscess may arise, especially after influenzal infection.

Metastatic abscesses cause acute manifestations and progress quickly to death. The diagnosis depends on the recognition of the rapidly increasing signs of intracranial pressure, associated with a source of possible septic embolic infection. In rare instances metastatic abscess runs a chronic course and may produce symptoms many months before the terminal events.

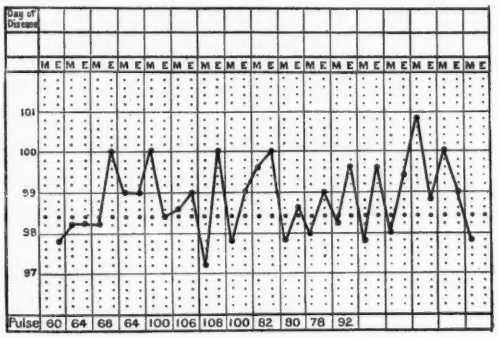


FIG. 6. Large multilocular metastatic abscess of centrum ovale.
R. F., aged 23. Patient drowsy on admission; pain in front of head; soon developed l. hemiplegia and double optic neuritis; r. pupil > l. with sluggish reactions; history of septic finger; operation; temporary recovery but final exitus.

Diagnosis from tumour. Difficulty arises if there is the combination of signs of tumour with a cause for abscess. Many mistakes have been made under such circumstances, and the error may be unavoidable; thus a patient with an old-standing left-sided foetid otorrhoea rapidly became drowsy and semi-comatose, and developed characteristic signs of temporo-sphenoidal lesion; subsequent events proved the lesion to be a tumour. Again, traumatism may either aggravate the growth of a pre-existing tumour, or possibly be the actual exciting cause of tumour. The diagnosis can only be indicated by a consideration of the nature of the injury, the history of any septic condition, and the contrast between the usually slow steady growth of a tumour, with the more abrupt and rapid progress of the manifest stage of abscess. Optic neuritis is more frequent in tumour than in abscess and reaches a greater degree of swelling. An absolute leucocytosis with the polymorphonuclear cells equalling 80 per cent. or more is often found in abscess and other forms of intracranial suppuration.

Diagnosis from other suppurative intracranial conditions. (1) *Simple purulent otitis* may, especially in children, give rise to grave cerebral symptoms, such as fever, drowsiness, rigidity of the neck, and alteration in the pupils; all these symptoms may disappear on simple puncture of the tympanic membrane.

(2) *Optic neuritis* with signs of intracranial pressure and even paralysis of one or both abducens nerves may be present with otitis media. Various explanations have been given for this symptom group. It has been attributed to local basal pachymeningitis, infection passing along the carotid sheath via the lymphatics to the optic nerve sheath, or to sinus thrombosis or meningitis serosa. Complete recovery may occur without intracranial operation. (3) *Extra-dural abscess.* The symptoms resemble those of brain abscess, and the diagnosis may be impossible, though in extra-dural abscess there may be a rigor and a continuous fever with temperature from 101° to 103°. In practice the extra-dural abscess is recognized by the surgeon during operation.

In otitic cases the most helpful diagnostic symptoms are pain in the ear or headache,—'cerebral otorrhoea'—i. e. sudden increase of the flow of pus and its long continuation when unexplained by the ear condition. Probably optic neuritis does not occur in uncomplicated extra-dural abscess, and, except in the traumatic variety, focal signs are uncommon, though such may develop from pressure on the cerebellum or temporo-sphenoidal lobe. (4) *Subdural abscess (ulceration of the brain)* is a cortical abscess and may give focal signs. There may be signs of meningitis, such as stiffness of the neck, fever, or delirium, but the cerebro-spinal fluid does not show the evidence of *general diffuse meningitis.* (5) *Sinus thrombosis.* There are the well-known external signs if the jugular bulb and veins are invaded, and chemosis, exophthalmos, neuralgic and supra-orbital pain, and oculomotor paralysis if the cavernous sinus is thrombosed. Constitutionally the condition is characterized by recurrent rigors with a swinging temperature from 98° or 97° to 104° or 105°, rapid pulse, vomiting, sweatings, and diarrhoea. Optic neuritis is frequent (30–50 per cent.).

The combination of external signs with constitutional symptoms determines the diagnosis. In practice the diagnosis is often made first during the operation. It is a valuable rule to suspect this condition, if with free egress of pus there is a high fever, provided diffuse meningitis can be excluded. A coexisting abscess may depress the pulse-rate. (6) *Meningitis.* The diagnosis of abscess has to be considered from local or diffuse purulent meningitis, and from serous meningitis.

(*a*) *Condition of the cerebral spinal fluid.* In suppurative meningitis this is characteristically turbid from excess of leucocytes. It is usually under pressure, contains excess of proteids, the alkalinity is diminished, and it does not reduce Fehling's solution. Micro-organisms may be demonstrated.

In serous meningitis the fluid is clear under pressure, sterile, or perhaps contains a few micro-organisms of low virulence. There may be a small excess of lymphocytes and only slight increase of proteid. Its reducing power, if present, is diminished. In the rare cases in which ependymitis is present without meningitis the fluid from ventricular puncture (in infants) may show distinct inflammatory changes, and be either sero-purulent or purulent, and at the same time the fluid from lumbar puncture may be clear. As a rare event in purulent meningitis, the communications at the base of the brain may be blocked and the lumbar puncture fluid appear normal. There will not be in such cases any

excess of fluid. In rare cases of abscess of the brain, sinus thrombosis or extra-dural abscess, the fluid may be somewhat cloudy from leucocytes, and even contain micro-organisms, without associated purulent meningitis, and such cases may recover.

(*b*) *Symptoms.* In general, abscess is indicated by a slow pulse, nearly normal temperature, mental dullness and hebetude, gradually increasing drowsiness, evidence of intracranial tension, and often signs of a circumscribed lesion; purulent meningitis, by high fever and rapid pulse-rate, signs of meningeal irritation at the base or convexity of the brain or of the spine. In children, abscess gives the signs of meningitis more commonly than in adults. In rare cases a diffuse meningitis may by a local intensity call forth focal signs and thus simulate brain abscess.

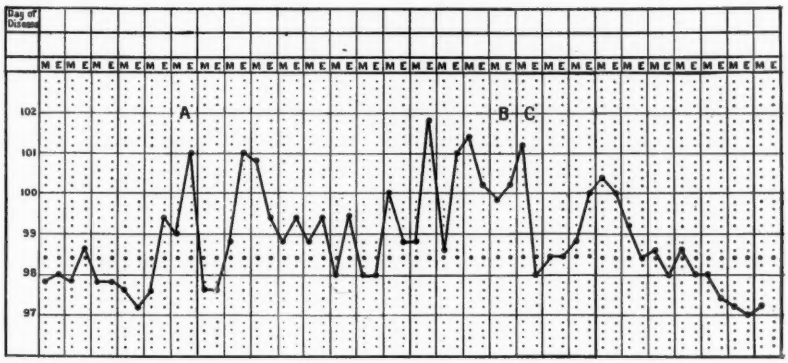


FIG. 7. Purulent labyrinthitis. (*Care of Mr. Hugh E. Jones.*)

Mrs. O., aged 35. L. otorrhoea for 1 year; radical mastoid operation; hearing good; caloric test normal.

(A) Pain in head first time since operation; continued from time to time; occasionally severe; no other symptoms; leucocytosis 18,000.

(B) Loss of hearing l. side and absence of labyrinthine response to caloric stimulus.

(C) Purulent labyrinth exposed; recovery.

The diagnosis of suppurative diffuse meningitis is in otitic cases to be made with considerable caution, for, excepting the findings of gross changes in the cerebro-spinal fluid, the symptoms may be very fallacious guides.

Serous meningitis and inflammatory oedema of the brain may produce the symptoms of purulent meningitis or brain abscess. The pulse and temperature do not show a marked deviation from the normal. There is no great prostration. Optic neuritis sets in rapidly and the swelling of the disks is marked. All the signs of meningitis serosa may rapidly disappear after removal of the septic focus, or after a decompression.

Diagnosis from labyrinthitis. The state of the hearing is to be observed, the functional tests for the labyrinth applied, and an attempt made to elicit the reaction movements of Baranyi. For information on these matters special works should be consulted. The following statements may, however, be made. Com-

plete or marked nerve deafness occurs in manifest purulent labyrinthitis, with fever and acute symptoms, and in the afebrile, symptomless, latent purulent labyrinthitis; in diffuse serous meningitis; in old-standing cases where the labyrinth structure is replaced by fibrous tissue or new bony formation; and in retro-labyrinthine disease of the cochlear nerve.

Partial nerve deafness occurs in circumscribed and serous labyrinthitis. Spontaneous nystagmus may be present in either labyrinthitis or cerebellar abscess, and is due in both cases to disharmony of the impulses from the semicircular canals. It is a reflex, and the arc is by the vestibular nerve to the Deiters' group of nuclei and their intricate connexion with the oculomotor centres. The reflex path is bilateral, each labyrinth being in relationship with the central nuclei of the muscles of both eyes. In nystagmus there is a slow component which is the vestibular reaction and a rapid return movement, and it is according to the direction of this that the direction of the nystagmus is named. A spontaneous nystagmus may be present in any form of labyrinthitis. It is usually rotatory and horizontal in type, and is directed towards the sound side and becomes more obvious by lateral deviation of the eyes towards that side. This is probably due to the unbalanced action of the normal labyrinth. A nystagmus directed solely towards the diseased side is rarely observed in labyrinthitis, and if there is nystagmus to both sides, this is evidence of incomplete destruction. With the progress of the disease it tends to disappear.

In abscess, on the contrary, though there is a fine nystagmus towards the contralateral side, the well-marked nystagmus is towards the side of the lesion and lasts throughout the duration of the disease. If labyrinthitis and abscess coexist, the cerebellar nystagmus tends to overpower that of labyrinthine origin. The application and interpretation of the functional tests in the diagnosis between labyrinthitis and abscess is not easy, and requires special experience. As the patients are usually confined to bed, the water test is used, and it is simpler to test only for the functional activity of the external semicircular canal. For this purpose the head is tilted backwards 60° and inclined 45° to the side about to be tested. Water at about 27° is used, and failing the special otocalorimeter an ordinary ear syringe may be used. A pure horizontal nystagmus towards the unsuspected (non-affected) side results if the labyrinth is functionating, and hence points to the cerebellum as the site of disease. If there be already a spontaneous nystagmus it appears best to use hot water (110° F.). It has already been mentioned that in labyrinthitis the direction of the nystagmus is towards the sound side—a point itself against the cerebellum being the primary cause. Then the caloric reaction aroused by the hot water will, if the labyrinth be functionating, abolish the pre-existing nystagmus.

If, however, it remains unaffected the possibility of abscess of the cerebellum must be carefully considered.

The labyrinthine responses are completely absent in manifest or latent purulent labyrinthitis or old-standing fibrous change.

The disturbance of equilibrium from labyrinth disease may be very great,

and in any rapid progress of the disease is far more obtrusive than is seen in cerebellar disease. It however rapidly diminishes in contrast to cerebellar incoordination, which may be observed so long as the condition of the patient permits.

The homolateral atonia which occurs in cerebellar lesion often causes the patient to tend to fall to that side, i. e. if there be a spontaneous nystagmus towards the side to which it is directed.

On the contrary, in labyrinthine disease, the disturbance of equilibrium depends upon the position of the canals, and hence varies with the position of head.

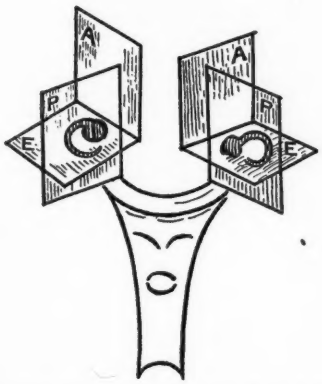


FIG. 8. Planes of the semicircular canals as seen from behind. (*After Ewald.*)

Other reactions, such as the pointing tests of Baranyi, have not yet, in the opinion of the writer, been sufficiently often compared and contrasted to permit of useful diagnostic information between cerebellar and labyrinth disease. Baranyi states as a principle that all the faulty movement reactions in labyrinth disease are in the direction of the slow component—the vestibular reaction—of the nystagmus.

Diagnosis from certain constitutional states. Some difficulty may arise when the acute cerebral signs of a specific fever coexist in a patient suffering from chronic otitis; notably this is so with influenza and typhoid fever. Chronic uraemic poisoning, if associated with otorrhoea, also introduces difficulties.

Prognosis and Treatment.

Abscess in the brain may disappear by natural drainage or undergo calcareous transformation, but practically speaking an untreated abscess is fatal. Heimann's table shows the much greater mortality of the complicated cases. Even with the best surgical treatment the prognosis is always grave. The patient may die after the diagnosis is made but before the operation, either suddenly from respiratory failure, or from rupture of the abscess into the

ventricle or extension to the meninges. Death may occur from the operation itself, or from complications following the operation. In Heimann's statistics there were 37 per cent. of cures out of 519 operations. In Körner's 50 per cent. of cerebral abscesses and 52 per cent. of cerebellar abscesses were cured. In Oppenheim's collection of 206 operations on otitic cases 70 per cent. of cerebral abscesses were successfully treated and 45 per cent. of cerebellar. Of 102 cases of cerebellar abscesses collected by Dench and submitted to operation 32 recovered; of 100 cerebral abscesses recovery occurred in 52 per cent. No doubt there is much overlapping in these statistics, and observations recorded by individual observers are valuable. Such very successful results are not in accord with experience generally in this country.

Heine observed 40 cases of brain abscess in Berlin from May 1894 to March 1906; 28 were operated upon, and in 12 the abscess was found at the section; in 22 cases the abscess was in the temporo-sphenoidal lobe. In all only 6 cases, i. e. 15 per cent., were cured. Macewen's results have so far not been surpassed by a single operator. The treatment is entirely surgical, and the rule is, in otitic cases, that unless the condition is urgent the tympanic cavity should first be explored, and an endeavour made to discover the tract of infection.

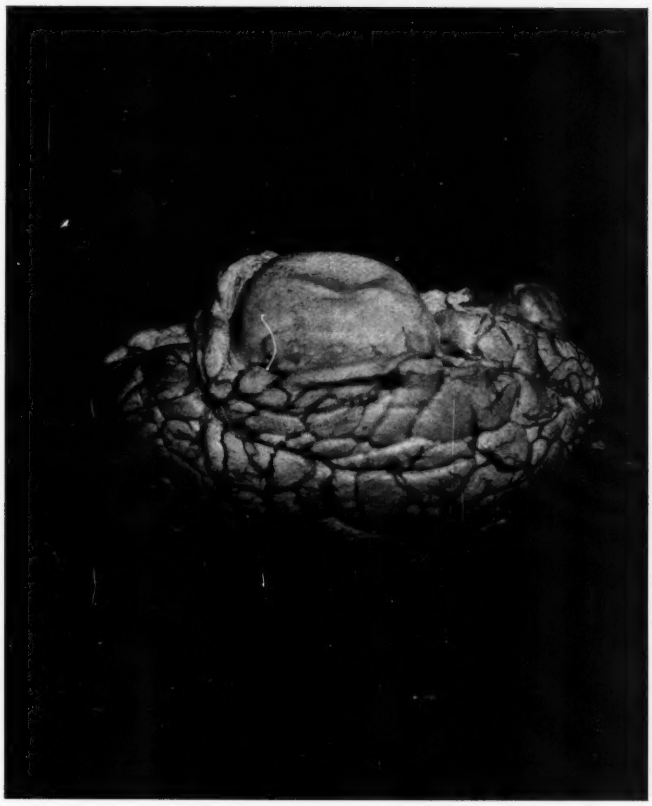
The writer begs to acknowledge the kindness of Mr. Wilfred Trotter and of his colleagues, Mr. Hugh E. Jones and Mr. Malcolm Stockdale, for permission to publish the charts illustrating their cases, and also to Mr. Hugh E. Jones for valued help in the preparation of this review.

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DESCRIPTION OF PLATE.

Right lateral aspect of the brain, showing an abscess of the temporo-sphenoidal lobe.



THE PATHOLOGICAL ANATOMY OF PRIMARY MEDIASTINAL SARCOMA

By G. T. HEBERT

With Plates 9–11

Sarcoma of mediastinal origin is entitled to study for two reasons. In the first place, it is, though rare, a definite clinical entity, a disease essentially of the lymphatic structures of the thorax, often difficult of diagnosis, especially in the early stages, when the treatment, at present tentative and inadequate, can be of most service. In the second place, its clinical resemblance to pulmonary tuberculosis, which is not infrequently very striking, may perhaps be due to a similarity in the method of extension of the two diseases; and it is not unreasonable to suppose that the study of this process in the invasion of the lungs by a mediastinal sarcoma may throw light on the similar problem in the case of pulmonary tuberculosis, if it can be shown that the latter is, primarily at least, a disease of the lymphatic system.

Though such a conception does not yet meet with general recognition, it cannot be denied that lymphatic vessels and glands play an important part in the earlier stages of the disease in those cases in which bacilli enter the body through the mucous membranes of the alimentary canal, and of the mouth, nose, and throat. In adults, at any rate, clinical and experimental evidence supports the older view that inhalation is the most common way in which a patient contracts pulmonary tuberculosis, but the part played by the peritracheobronchial glands in the process is by no means conclusively determined. There is a tendency in recent years to regard them as increasingly important in this connexion, and to believe that, as suggested by Ribbert (1), a tuberculous process in them precedes the formation of the characteristic lesions in the lungs. It is, however, assumed that the bacilli travel from the glands to the lungs by means of the broncho-mediastinal trunk and blood-stream.

If the inhalation theory and Ribbert's observation are correct, it is probable that, in the majority of cases, bacilli contained in the inspired air penetrate the walls of the air passages or alveoli but leave them unaffected, and are carried by the normal lymphatic paths to one of the groups of the peribronchial glands, where they are arrested and where they initiate a tuberculous process. The resultant fibrotic changes, which in some cases check the disease temporarily or

TABLE I.

Showing the History and Chief Pathological Findings of 26 Cases of Primary Mediastinal Sarcoma.

A '+' sign denotes the presence, a '0' the absence, of a symptom or pathological condition: a '—' that neither were recorded.

	Initials.	No. of Case.	Sex.	Age.	Duration, in months.	Dyspnoea.	Wasting.	Haemoptysis or Staining.	Pain.	Night-sweats.	Survived after Admission.	Other Symptoms.	Lung affected.	Pleural Effusion.	Purulent Bronchitis.	Cervical Glands.	Heart.	Pericardium.	Pericardial Effusion.	Superior Vena Cava.	Oesophagus.	Secondary Deposits.	Other Disease.
Group I. 'Diffuse' type.	F. A.	1	M.	21	6	—	++	0	+	0	1 week	—	R. & L.	R. & L.	0	R. & L.	0	+	0	—	0	0	Sternum said to be eroded by growth
	E. S.	11	F.	40	3	++	+	—	—	—	2 months	—	R.	R.	+	R.	0	0	0	—	—	Retro-aortic glands and pancreas	—
	H. E.	12	M.	34	2	+	+	Staining	+	—	7 weeks	—	R.	—	—	R.	0	0	0	—	0	Liver and gall-bladder	—
	G. B.	13	M.	44	4	+	++	Staining	—	—	2 weeks	—	L.	L. small	+	0	0	+	—	—	0	Liver and lumbar glands	—
	A. P.	15	F.	53	3	+	+	0	+	—	2 months	—	R.	—	—	—	0	+	0	+	+	Liver, omentum, and meso-appendix	—
	G. M.	18	M.	37	4	+	+	Staining	+	+	1 month	Oedema	R.	R., 3½ pints L., 2 ,,	+	R.	0	+	0	+	0	0	—
	J. W.	19	M.	65	4	+	++	Staining	+	—	1 hour	Dysphagia	R.	0	+	R.	Auricles	+	0	+	+	Kidney	—
	D. B.	20	M.	56	5	+	+	Staining	+	—	10 weeks	—	R.	L., ante-mortem	+	0	+	+	0	+	+	0	Hydatid cysts in mesentery and prostate
	R. S.	21	M.	49	2	+	+	Small haemoptysis	+	+	3 weeks	Aphonia Oedema	R.	R. & L.	0	R. & L.	0	0	0	+	0	Retro-aortic glands and pancreas	—
	A. T.	26	M.	37	2	++	+	0	+	0	6 weeks	—	R.	0	+	0	Auricles	+	0	+	+	0	Pulmonary tuberculosis, old, r.: recent, l.

Initials.	No. of Case.	Sex.	Age.	Duration, in months.	Dyspnoea.	Wasting.	Haemoptysis or Staining.	Pain.	Night-sweats.	Survived after Admission.	Other Symptoms.	Lung affected.	Pleural Effusion.	Purulent Bronchitis.	Cervical Glands.	Heart.	Pericardium.	Pericardial Effusion.	Superior Vena Cava.	Oesophagus.	Secondary Deposits.	Other Disease.
Group 2. 'Central' type.																						
A. B.	2	F.	42	6	—	+ +	Staining	+	+	3 months	—	L.	—	0	—	0	+	0	—	+	0	Old pulmonary tuberculosis, r.
M. D.	3	F.	37	12	+	+ +	Haemoptysis and staining	—	—	3 days	—	R.	—	0	—	R. auricle	+	+	+	—	0	—
T. R.	4	M.	28	3	—	+	Haemoptysis and staining	+	+	3 months	—	R.	—	0	—	R. auricle	+	0	+	0	0	—
S. G.	5	M.	29	3	+ +	+	Haemoptysis	—	+	2 months	—	L.	—	0	—	0	+	0	+	+	0	—
L. H.	10	F.	47	3	+ +	+	—	+	—	5 weeks	—	L.	—	0	—	0	0	0	—	0	0	—
M. H.	17	F.	33	12	+ +	+ +	0	+	0	1 month	—	R.	0	0	0	0	+	0	—	0	0	Acute endocarditis
T. E.	22	M.	46	6	+ +	+	Staining	0	0	5 weeks	Nodule in back	R.	0	0	0	0	+	0	+	+	Suprarenals. Muscle r. interscapular region	—
M. P.	23	F.	26	3	+	+	Haemoptysis and staining	+	+	3 months	—	R.	0	0	0	+	+	0	+	+	0	—
E. S.	24	M.	24	5	+	+	0	+	+	2 weeks	Ascites	R.	0	0	0	Auricles	+	0	+	+	0	—
Group 3. Indefinite.																						
E.H.*	8	M.	56	—	—	—	—	—	—	1 day	—	R.	—	+	R.	0	0	0	—	0	0	—
J. T.	16	M.	45	2	+	+ +	Staining	+	—	4 months	—	L.	—	—	0	0	0	—	—	0	Liver and spleen	—
C. E.	14	M.	31	6	+ +	+ +	Haemoptysis	—	+	9 months	—	R.	—	—	+	—	+	—	—	0	Pancreas	Pulmonary tuberculosis, recent, l. apex
D. T.	6	F.	21	2	+	+	0	+	0	1 month	Aphonia	L.	L., haemorrhagic	+	0	L. auricle	+	+	—	+	0	—
C. E.	7	F.	42	12	+	+	Staining	+	—	3 months	—	R.	—	+	0	R. auricle	+	+	—	0	0	—
W. J.	9	M.	49	5	+ +	+ +	Staining	+	—	2 weeks	—	R.	R., 2½ pints	0	R.	0	0	0	—	0	0	—
M. G.	25	F.	34	8	+	+	0	+	+	2 months	—	L.	L., 2 ,, ante-mortem	0	L.	L. auricle	+	0	+	+	0	Acute endocarditis

* No clinical notes available.

permanently, tend to involve the afferent vessels of the affected glands, causing retardation, obstruction, or reversal of the normal flow of lymph, and favouring, in consequence, the backward spread of bacilli from the root glands to the lung. Riviere (2) thus describes the process in hilus tuberculosis: 'The normal lymph flow . . . soon becomes obstructed in certain areas when tuberculosis of the lymphatic glands arises. Blockage of the lymph channels then leads to their distension, and finally to a backward flow, either directly from the incompetence of their valves, or indirectly through the free anastomosis of lymph channels in the lung, whereby the lymph is drawn outwards into neighbouring systems. In whichever way arising, the tubercle bacillus gradually travels outward from the glands, passing through the lymphatic wall as it goes, and setting up bronchopneumonic processes in the surrounding lung. If these heal, the resulting scars still further increase the obstruction, so that the disease passes slowly outwards mainly in the tissue round the bronchi and vessels.'

Such a theory offers possible explanations for several of the unexplained facts of the incidence of pulmonary tuberculosis. Birch-Hirschfeld (3) and Schmorl (4), for instance, agreed that early tuberculosis begins, as a rule, in bronchi of the fifth order, and inferred that the local lesion is due to the arrest of inhaled bacilli at this spot; but this is the place where, according to Poirier and Charpy (5), the outer bronchial network, traced outwards from the lung root, terminates, and where bacilli travelling backwards along the peribronchial paths would most probably be trapped. Again, Poirier and Charpy state that the peribronchial lymphatics of the upper and middle lobes drain into the peribronchial glands, but those of the lower lobe into the intertracheo-bronchial, or bifurcation, glands, a fact which may have some bearing on the preponderance of apical lesions. Further, the incidence of pleurisy and of pleural effusion may depend on abnormal conditions of the pulmonary lymphatic system, for in children a pleural effusion may be present when the bronchial glands are enlarged, but when no evidence can be found of tuberculosis in the lungs.

In cases of pulmonary tuberculosis few opportunities are afforded for the pathological study of this suggested process of outward extension of the disease, but in those of mediastinal sarcoma it is generally found that when death supervenes the invasion of the least affected lung is in quite an early stage. The thoracic contents from ten cases of primary mediastinal sarcoma were therefore investigated by dissection and microscopical examination. The results in the case of the least affected lung were somewhat inconclusive, and need verification from the study of further cases: for, without a differential stain for sarcomatous cells, it was not found possible to distinguish with certainty between an early deposit of malignant cells and a collection of round cells in a dilated lymphatic, or between early malignant and inflammatory changes in the wall of a bronchiole. But as the work illustrated several of the more important points in the pathological anatomy of primary mediastinal sarcoma, and revealed a few features not commonly recognized, the greater part of the following account is a summary of the relationship of the new growth to the different

intrathoracic structures, and of the resultant symptoms in their bearing on the diagnosis. The pathological anatomy of the disease well repays study. For though it is true that mediastinal growths may attain to a considerable size without causing any symptom, and, on the other hand, a tumour comparatively small but in an important position may produce profound distress, yet, in the majority of cases, not only can a diagnosis and a reasonable estimate of the size and position of the tumour be made, but also symptoms can be anticipated to a certain extent, provided that the pathological aspect of the disease is sufficiently well understood for the full interpretation of the symptoms and signs.

All of the material was obtained from the City of London Hospital for Diseases of the Chest, Victoria Park. To the ten cases numbered 17–26, which occurred in the years 1915–17, are added sixteen from the preceding seven years. The history and chief pathological findings are included in a table, as the descriptions sufficiently detailed to give a comprehensive account of the cases are too lengthy for publication. For permission to use the notes and post-mortem records of Cases 1–16, as well as for help and advice, I am indebted to the Pathologist and Registrar, Dr. S. Roodhouse Gloyne; and my thanks are also due to Dr. Hadley, Dr. Colbeck, Dr. Chaplin, and Dr. Williamson, Visiting Physicians, who kindly allowed me to make use of their cases.

Historical.

Though it is chiefly within the last twenty-five years that a true conception of sarcoma of mediastinal origin has been formed, owing largely to an increase in pathological knowledge, intrathoracic growths were recognized by writers in the seventeenth and eighteenth centuries, Bonetus, Boerhaave, Lieutaud, Morgagni, and others, but were regarded rather as pathological curiosities. In the first half of the nineteenth century Voigtel called attention to the connexion of the bronchial glands with the growth, Boyle recognized a cancerous phthisis, Burton laid down principles for its diagnosis, and Gintrac collected a series of cases; while Portal, Laennec, Sims, and Stokes wrote on the subject.

By 1865, the year in which Cockle published his book *On Intrathoracic Cancer*, the diagnosis had been placed upon a more sure footing, but the first complete account, which still remains one of the best on the subject, was produced in 1892 by the late Dr. Steven (6).

In dealing with primary mediastinal sarcoma from the clinical and pathological points of view, he differentiated it from lymphadenoma, in marked contrast with the American pathologists of the present day, who, by considering together lymphosarcoma, lymphadenoma, and lymphatic leukaemia as diseases of the lymphatic system, tend to obscure the clinical differences between them. He approved of the term 'lymphosarcoma', meaning thereby 'that variety of sarcoma which, both by its naked-eye appearances and by its histological

characters, is to be looked upon as originating in connexion with the lymphatic glands—i. e. a sarcoma of lymphatic glands'. Above all he pointed out the importance of a knowledge of the pathological anatomy of the disease.

In Allbutt and Rolleston's *System of Medicine*, Roberts (7), paying a tribute to the value of Steven's work, gives a full description; but, with this and a few other exceptions, the authors of modern books on medicine and on respiratory diseases are inclined to give to it less attention than it deserves.

Frequency.

It is not proposed to discuss the relative frequency of intrathoracic sarcoma and carcinoma, primary and secondary. In Hare's (8) tables, published in 1889, many of the earlier cases were, perhaps, incorrectly diagnosed as carcinomata, making the percentage of this variety of new growth considerably higher than that of sarcoma. Though no tables comparable to his but of more recent date have been published, it would seem that primary mediastinal sarcoma is at least as common as any other form of intrathoracic new growth.

The disease occurred in one in every 292 cases admitted to Victoria Park Hospital in the years 1908–17, while, during the period December 1915 to September 1916, seven cases of sarcoma and three of carcinoma, all originating in the mediastinum, were found in 571 admissions. These figures do not include cases on which no post-mortem was made. The frequency of the disease is, of course, greater in a special hospital for diseases of the chest than in a general hospital, and, as in other hospitals, the less common and less easily diagnosed cases have preference for admission.

Statistics.

Some interesting statistics of sixty cases of primary new growth in the mediastinum, admitted to the Brompton Hospital during the years 1900–13, have recently been published by Ross (9). Forty-four of them were proved to be sarcomata, but the figures given are derived from the whole collection of sixty cases, a fact which may account for some of the slight discrepancies in the comparison of the Victoria Park and Brompton figures which is given in Table II. It will be seen that the chief difference between the two sets of figures lies in the smaller number of cases of the Victoria Park series which presented secondary deposits in the abdomen, and in the greater number which showed growth in one lung only.

TABLE II.

	Victoria Park.	Brompton.
Relative frequency in cases admitted	1:292	1:350*
Proportion of male to female cases	1·6:1	2·15:1
Age of onset, over 30 years	77 %	85 %
" " 30 to 50 years	62 %	70 %
Situation of pulmonary disease, right lung	69 %	48 %
" " left lung	27 %	22 %
" " both lungs	4 %	23 %
Duration of the disease, average	30 weeks	32 weeks
" " minimum	11 "	9 "
" " maximum	66 "	88 "
Cases with secondary deposits in the abdomen	9	41
" " the liver	4	21
" " pancreas	3	4
" " suprarenals	1	10
" " spleen	1	7
" " kidneys	1	7
Cervical glands involved in	10	
Situation of non-pulmonary intrathoracic disease—		
in the pericardium	19	
pericardial effusion	4	
in the S. V. C.	13	
in the oesophagus	10	
in heart muscle	10	

* Percentage calculated for the sarcomata of the series.

Symptoms.

Reports of cases of mediastinal sarcoma in English and foreign literature are numerous, and show considerable differences in the prominence and date of occurrence of the chief symptoms; in fact it is for this reason that many are published. The following conclusions are derived chiefly from the study of the twenty-six cases of this series.

Dyspnoea is the most prominent symptom, and is often out of all proportion to the amount of lung tissue involved. It was present in all of the cases, and in the majority was very marked. It is due to one or more of the following causes:

1. Oedema and engorgement of the mucous membranes of the trachea and bronchi.
2. Compression of the trachea and bronchi.
3. Destructive and fibrotic changes in the lung.
4. Oedema of the larynx, and paresis of the cords.
5. Pericardial and pleural effusions, bronchopneumonia, &c.
6. Cardiac dilatation.
7. Temporary plugging of the bronchi with mucus.
8. Irritation or paralysis of the vagus, sympathetic, or phrenic nerves.
9. Stimulation of the respiratory centre by deficiently oxygenated blood.

The last three factors are chiefly operative in the paroxysmal attacks that are often seen, especially in the earlier stages, and may be contributory to the other six, which are placed in the order of their importance. The onset of dyspnoea is generally gradual, but cases have been recorded in which it was so sudden as to suggest pneumothorax.

Cough is generally a prominent, and often the earliest, symptom; and its character in many cases depends on laryngeal paralysis or on compression of the trachea and bronchi. The amount of *sputum* is, as a rule, small, and less than in cases of pulmonary tuberculosis. Malignant cells can occasionally be recognized in it.

Haemoptysis is said to be an unimportant symptom, but it was recorded in 24 per cent. of the cases. It was not, however, severe. Persistent staining of the sputum, due either to congestion of the respiratory passages or to destruction of lung tissue, was more frequently seen (in 52 per cent.). Blood in one or other form was coughed up in 64 per cent. of the cases.

Loss of weight, though not so pronounced as in most cases of extrathoracic malignant disease, is almost invariably present to a greater or less extent. A patient with a history of symptoms for three months will probably be found to have lost at least a stone in weight. About 35 per cent. of the cases showed a greater degree of wasting than this. Ross, however, states that in many of his cases true wasting was absent.

Night-sweats were present in 36 per cent. of cases, and seemed to bear no relation to pyrexia. The latter, if present, is caused by complications such as tuberculosis, purulent bronchitis, or bronchopneumonia.

Pain is a common complaint, but, since its cause is not the same in each case, varies considerably in character and acuteness. Pleuritic pain is often very persistent and rather definitely localized, but friction is rarely heard. Post-sternal pain and a sense of constriction probably indicate a mass filling the mediastinum. In some cases the pain is dull and located on the unaffected side of the chest: in others it amounts merely to a sense of uneasiness or fullness. Pain from pressure on the brachial plexus and on intercostal nerves is more common in carcinomatous cases.

Cyanosis, venous dilatation, and oedema form an important group of symptoms. In cases of growths originating in the superior mediastinum they are early and prominent. In the majority of cases they occur at a later date, and are often followed by a marked deterioration in the condition of the patient. The veins most commonly affected are those on the face and neck, on the front of the chest and just above the costal margin, on the shoulders and arms, and in the lumbar region. Oedema soon follows the dilatation of these veins, and has the same distribution. At first transitory and present perhaps only in the recumbent position, it becomes more persistent and extensive, and, if it involves the larynx, considerably aggravates the existing dyspnoea.

Dysphagia, hoarseness, and contracted pupil are not uncommon, and may be among the earlier symptoms.

Vomiting and hiccough, the latter from involvement of the phrenic nerve, are more rarely seen.

Coma, delusions, and mental derangement occur in the later stages.

The symptoms due to *metastatic deposits* in the abdomen are few, and occur late. Cerebral metastases, when they occur, are more important.

Origin.

Primary mediastinal sarcoma arises in the lymphatic glandular structures of the thorax, that is, the thymus and the lymphatic glands, except in the cases of the rarer forms of sarcoma such as lipoma sarcomatodes and osteo- and chondrosarcoma, and in the cases of growths of subpleural origin which should really be classed as endotheliomata. In the majority of cases origin from the thymus is difficult to prove, but may sometimes be definitely established, as in two cases recorded by Sheen and others (10) in 1911. Thymic tumours, which are said to be more common in children, should show concentric bodies, in which there are large central cells surrounded by flattened cells. They are composed chiefly of small round cells, and are, as a rule, very vascular. Some which resemble sarcomata are probably small spheroidal-celled carcinomata.

Though the anterior mediastinum as defined in Gray's text-book of anatomy contains only a few glands, it is said to be the most common seat of the primary disease by Hare (8), Wilson Fox (11), Ross (9), and most of the other observers who give an opinion. They, no doubt, include in the anterior mediastinum the division described as the superior, with its important groups of glands round the arch of the aorta and round the innominate veins.

It is often very difficult to determine at the post-mortem where the disease has arisen, and no figures can be given for Cases 1–16. But in Cases 17–26, taking into consideration the clinical aspects as well as the post-mortem findings, the bifurcation and bronchial glands, which lie at the posterior and superior limit of the middle mediastinum, were the most probable seat of the primary disease in five cases, the posterior mediastinal glands in four cases, and the superior in only one.

Spread.

Starting in a gland the new growth enlarges, both by extension along lymphatics to neighbouring glands and by breaking through the capsule and invading surrounding connective tissue, to form an irregularly lobulated tumour which increases in size in the direction of least resistance. In Steven's words, 'bulky and lobulated as most lymphosarcomata of the interior of the thorax are, they do not simply crush the organs aside, as many other varieties of tumour would do. You find processes of growth peeping out beneath the arch of the aorta, pushing their way upwards beneath the clavicles into the triangles of the neck, insinuating themselves between, and applying themselves around,

the great blood-vessels of the root of the neck and bronchial stems; and all this without there necessarily being any actual incorporation of the surrounded structures and tissues into the substance of the tumour itself, at least in the first instance.'

In the anterior and posterior divisions of the mediastinum masses of considerable size may cause only slight retraction of lung or displacement of heart, but in the middle and superior divisions the new growth, 'moulded around the great tubular and vascular structures of the upper portion of the thoracic cavity', soon makes its presence felt. Though the process is essentially a cell proliferation rather than a destruction of normal tissues, a local malignant action is seen, especially in the case of the bronchi, and, to a less extent, in that of the veins.

Outward extension along the course of the main bronchi to the lung is especially evident, so that in almost all cases there is, at the time of death, invasion of pulmonary tissue. But it is remarkable in this connexion that, at any rate in the cases of the Victoria Park series, only one lung (more frequently the right in the proportion of 18 to 7) was invaded. The opposite lung showed growth extending into the root and perhaps to the pulmonary glands, and it was congested and oedematous, but no growth could be seen in the tissue of the lung itself. The argument that involvement of one lung causes death before there has been time for the invasion of the other is probably fallacious, for there was a considerable difference in the degree of involvement of the affected lung. In Case 21 it amounted merely to a sector of the right lung; and the fatal factor in this and in other cases was not the size, but the position, of the growth and the resultant obstruction of the superior vena cava.

A third form of spread is by metastasis. If a vein has been pierced deposits may occur in the abdominal viscera, or in the lungs, brain, or subcutaneous tissues.

Macroscopic Appearance.

The more rapidly growing of these tumours are, as a rule, soft and white, exuding a milky fluid on section. Small haemorrhages are often seen in the deeper parts, and generally some pigmented glandular remnants. There is usually an ill-defined capsule, continuous with the connective tissue stroma of the growth. Small grey or dull yellow areas of degeneration are present, especially in the more fibrous, more slowly growing tumours, some of which are of a daffodil yellow colour.

The metastatic deposits and the secondary extensions sometimes show the true features of the growth better than do the mediastinal glands. Degeneration is especially common in the pulmonary growth, owing no doubt to superadded septic infection.

Microscopic Appearance.

Microscopically, the twenty-six cases of the series presented very similar characteristics. The cell common to all was an oval cell rather larger, sometimes much larger, than the lymphocyte, but, like it, possessing little cytoplasm. The nucleus has a capsule which sometimes appears to be rather shrunken, and it stains less deeply than does that of the lymphocyte. It contains a granular network and a well-marked eosinophil nucleolus. The cells are sometimes seen in pairs, and lie in a delicate connective tissue reticulum. Spindle cells, giant cells, and cells resembling the myelocyte were present in small numbers. In Case 22 spindle cells were predominant.

More or less degeneration was shown in all of the cases, the cells in the degenerated areas being ill-defined and not stained by haematoxylin.

The Relation of the New Growth to the Different Intrathoracic Structures.

The lungs. Primary mediastinal sarcoma invades the lung, in the majority of cases, by extension from the mediastinal glands, but it appears to do so in two different ways, so that, in characteristic cases, very different post-mortem appearances are produced, while in others an intermediate condition inclining to one or other extreme is seen.

The essential naked-eye characteristic of the first group is the tendency of the growth to spread outwards along the line of the bronchial tree to the surface of the lung, where it forms well-marked deposits in the subpleural tissues. The bronchi stand out as thick white strands, showing inflammatory changes and dilatation. The pulmonary glands are visible, but are only slightly enlarged and only partially replaced by growth. Invasion of lung tissue takes place, especially near the surface and at a depth of an inch to an inch and a half. Early growth is often subpleural and perivascular, but later there is a diffuse infiltration, so that in the advanced stage the whole of a lobe may be affected, small islets of lung tissue remaining, or perhaps only a fibrous framework containing blood-vessels and bronchioles. Though the subpleural tissues are attacked early, invasion and perforation of the visceral pleura occurs much later, if at all. In Case 21, which demonstrated the condition very well, the growth was almost entirely confined to the right middle lobe. Several large masses had formed beneath the pleura, which were as dense as the deposits in any other part of the affected sector; early perivascular deposits were found in the other lobes. The illustration of Case 26 (Plate 9) shows the appearances of the different stages. The growth is oldest at the base of the lung, and comparatively recent at the apex, where there are also some changes due to antecedent arrested tuberculosis.

Cases falling into the second group are probably of more frequent occurrence, and give the condition usually described in text-books. A solid, firm, nodular, sharply defined mass spreads into the affected lung from the root, generally into the lower lobe, leaving a cap of compressed lung apparently free from growth.

The outlines of much enlarged pulmonary glands can be seen especially near the growing edge. The bronchioles of the compressed cap are only moderately dilated, and a purulent bronchitis is rare. Areas of haemorrhage are common, especially in the upper lobe just above the interlobar septum. The pleura and subpleural tissues are unaffected unless the growing edge has reached them, in which case the pleura is thickened and often pierced. This type may be called the 'central' as compared with the 'diffuse' type. The illustration of Case 24 (Plate 10) shows the characteristic appearance of central growth, and in the outer part of the lower lobe there is advanced infiltration of the diffuse type. In Cases 18 and 25 there was evidence of both processes, with central growth predominant in one and subsidiary in the other.

It was also noticed:

1. That growths which have originated in the posterior mediastinum invade especially the lower lobe of the right lung.

2. That the mediastinal mass is nodular and circumscribed in cases of central growth, but surrounded by a fringe of partially invaded glands in those of the diffuse type.

3. That macroscopic growth is rarely seen in the tissue of the least affected lung, though invasion of the peribronchial and pulmonary glands is common.

The difference between the two types is sufficiently striking to warrant a careful consideration of the underlying cause.

It is possible that the growth differs histologically in the two cases, but microscopical examination did not lend any support to this view. The cell with the oval nucleus, already described, was predominant in every case but one, and the microscopical appearances were remarkably uniform. In Case 21, a good instance of the diffuse type, the cells more closely approximated to the lymphocyte than in any others of the series, while the spindle-celled sarcoma gave the appearance of central growth.

The distribution of the growth, as, for instance, in Case 26, is enough to exclude a miliary invasion from the blood-stream.

It is therefore more probable that the true explanation is to be based on the anatomy of the lymphatic system. Invasion of one set of lymphatic vessels, e. g. the perivascular, might give rise to a diffuse growth, and of another set, e.g. those from the parenchyma, to a central growth. Or, the diffuse type might be caused by spread along lymphatics, the central by direct invasion of the lung by the growing edge of the original mediastinal mass.

To decide between the two necessitates a consideration of the pulmonary lymphatics. According to Poirier and Charpy (5) the main trunks are:

1. Superficial, arising from the superficial perilobular network, and draining the visceral pleura.

2. Deep, accompanying the bronchi and vessels. The peribronchial trunks drain the alveoli by means of the alveolar, intralobular, and interlobular vessels, and the bronchial networks; the perivascular trunks drain the subpleural network.

The bronchial networks are two, an inner in the larger bronchi and an outer

which reaches to the terminal bronchioles. There is a free anastomosis between the peribronchial and perivascular trunks, and between them and the superficial trunks. The latter, however, is denied by Miller (12). The subpleural network does not connect directly with the intralobular and interlobular lymphatics.

The superficial trunks drain into the bronchial glands, the deep pass through the pulmonary glands on their way to the bronchial. It is stated that the peribronchial trunks from the upper lobes drain into the peribronchial glands, and those from the lower into the bifurcation glands. This observation, if correct, provides an explanation of the invasion of the lower lobe by growths originating in the posterior mediastinal glands, which are closely connected with those below the bifurcation.

Sections from the periphery of the lung show that growth of the diffuse type is often, if not always, perivascular and subpleural, at least in the first instance, a combination in accordance with the facts that the perivascular lymphatics drain the subpleural tissues or spaces, and that the outer bronchial network extends no farther than bronchioles of about 2 mm. in diameter. Deeper in the lung the bronchial walls suffer severely, but it is only rarely possible to demonstrate that growth is invading the alveoli from the peribronchial region.

In cases of the central type the growth is separated from the lung outside by a firm fibrous capsule, which in some cases appears to be the hypertrophied capsule of a pulmonary gland. Proximal to it and continuous with it is often a framework resembling that of a gland, filled with malignant cells. In places the capsule is pierced and invasion of the walls of neighbouring alveoli is taking place. The alveoli distal to the capsule are either compressed or filled with 'catarrhal' cells. Areas of haemorrhage are seen, and a moderate dilatation of the bronchioles, but inflammatory changes in the walls of the latter are rare. Definite perivascular invasion, usually in an early stage, is sometimes present in the lung between the capsule and the pleura.

The evidence therefore suggests that on reaching a gland at the root of the lung the growth either replaces it, enlarges it, and finally bursts through its capsule to invade the surrounding tissue and neighbouring pulmonary glands: or else passes through it with comparative ease, extends along peribronchial lymphatics to the next gland, where the same process is repeated, and finally reaches the peripheral perivascular lymphatics, from which it invades the subpleural tissues. It also forms deposits deeper in the lung, probably at the origin of the peribronchial trunks. When growth in these two situations has blocked the main channels, the perivascular and the peribronchial, invasion of the smaller vessels, those from the parenchyma, takes place. The second of these two processes, which gives rise to growth of the diffuse type, presents the greater resemblance to tuberculous invasion of the lungs. The resemblance was, in fact, very striking in Case 26, where early arrested tuberculosis and early malignant invasion were seen together in the right upper lobe. It is possible that the central type is also analogous to tuberculosis—to the 'hilar' type.

An attempt was made in Table I to classify the twenty-six cases from the post-mortem appearance of the lungs: in Group 1 are placed ten cases in which were recorded the presence of subpleural masses, of definite radial spread, or of malignant thickening of the bronchi, provided that no mention was made of a solid mass at the root of the lung. Nine cases were found in which the characteristic picture of central growth was described. In the remaining seven cases the description was not sufficiently exact to warrant inclusion in either group, or central and diffuse growth were both present and it could not be ascertained which was older or predominant. The first three, however, probably belonged to Group 1, the latter four to Group 2.

From Table III, which gives some statistics of the two groups, it appears that spread along the lymphatics occurs in older people, is more rapidly fatal, is accompanied by purulent bronchitis, by pleural effusion, and by enlargement of cervical glands, and gives rise to secondary deposits in the abdomen, in marked contrast to cases of Group 2 in these respects. The reason for the latter two characteristics is not obvious: there is said to be no anastomosis between the jugular and broncho-mediastinal trunks. Clinically, cases of Group 1 give earlier and better-marked physical signs, because the growth is nearer to the surface.

TABLE III.

	Group 1.	Group 2.	Group 3.	All Cases.
Number of cases	10	9	7	26
Sex, male	8	4	4	16
„ female	2	5	3	10
Average age	44	35	40	40
Duration, before admission	4 months	6 months	6 months	5 months
„ after admission	5 weeks	8 weeks	12 weeks	8 weeks
Cases with haemoptysis	1	4	1	6
„ staining	5	2	3	10
„ both	0	3	0	3
Cases with pleural effusion	6	0	2	8
„ purulent bronchitis	5	0	3	8
„ enlarged cervical glands	6	0	4	10
„ secondary deposits	6	1	2	9

The lung may be invaded in two other ways:

1. By direct invasion from the mediastinal surface of the pleura.
2. By metastasis, i. e. miliary invasion.

The former is seen sometimes in conjunction with invasion from the root of the lung. It is probably more common in carcinomatous growths. Metastatic nodules in the lungs were not seen in any of the twenty-six cases, but instances are given in the literature of the subject.

The pleura. Pleural adhesions are almost invariably present. Those on the same side as the pulmonary growth are firm; those on the opposite side are recent and easily broken down, or in some cases altogether absent.

Malignant invasion of the pleura occurs:

1. In cases of diffuse growth, in the later stages.

2. In cases of central growth, if the whole of the lung tissue from root to pleura has been destroyed; but where a cap of compressed lung remains the pleura is apparently normal.

3. By direct invasion from a growth applied to the mediastinal surface, above or below the root of the lung.

4. Very occasionally by metastasis.

The invaded pleura is found to be thickened and vascular, crowded with small round cells in thin-walled vessels (probably lymphatics) and between the connective tissue fibres.

In Cases 24 and 26 the right lower lobe was extensively destroyed, dense growth being found in the lung subjacent to that part of the mediastinal pleura which is related to the parietal pericardium. The latter was firmly adherent to the pleura, and presented a granular mottled surface in Case 24, an instance of central growth; but was unaffected in Case 26. This tendency of growths of the central type to pierce the pleura was noticed in other cases also.

The existence of pleural stomata described by some anatomists (e.g. Cunningham, 1906, 983) is denied by Poirier and Charpy, who figure the distal ends of the subpleural lymphatics as closed. Were stomata present it would be expected that the pleural sac would be invaded from malignant subpleural deposits, or even before these deposits were formed. The relative immunity of the pleura in cases of diffuse growth is therefore evidence against the existence of stomata.

Pleural effusion was present at the post-mortem in eight cases, in three of which it was bilateral; and in two other cases an effusion was found on exploration, but disappeared before death. Transitory effusions probably occur in the majority of cases in the early stages of the invasion of the lungs; and, perhaps, small effusions shortly before death. The percentage of cases with pleural effusion is smaller than the 52 per cent. found by Ross (9). Only 1 of the 10 was haemorrhagic, whereas Ross found 15 out of 29.

The air passages. The trachea suffers, especially at its lower end, in almost all cases of mediastinal sarcoma. It may be pushed to one side, compressed, invaded, and, occasionally, perforated. A growth, enlarging so as to come in contact with it, soon becomes adherent, and invasion of the tracheal wall commences. The structures of the wall are progressively destroyed, the cartilage showing a high degree of resistance, until the mucous membrane is invaded and ulcerated. Ulceration is, however, comparatively rare, but inflammation and oedema are common.

The main bronchi are found, generally, to have suffered severely. That on the affected side may be almost occluded, and all traces of the component parts of the wall, except the cartilage, destroyed, so that it appears as a narrow track in the growth, filled with purulent material and malignant débris, and lined by soft

ulcerated surfaces. That on the opposite side generally shows narrowing and considerable replacement of the wall, but growth can rarely be traced beyond the second bifurcation.

The smaller tubes on the affected side show dilatation, with or without purulent bronchitis, round-celled infiltration, or malignant invasion. The dilatation is due to narrowing of the main bronchus, with malignant invasion of the wall and loss of tone from the destruction of the nervous supply as predisposing factors.

The fact that the bronchi are provided with lymphatic networks, the larger with two and the smaller with one, is no doubt the reason why they are so commonly and so extensively invaded by the growth. The bronchioles near the surface of the lung are not affected by growth, owing to the fact that the outer network does not extend beyond bronchioles of about 2 mm. in diameter.

The veins. The way in which sarcoma invades veins was studied chiefly in the superior vena cava.

The outer coat of a vein soon becomes adherent to a growth with which it comes in contact. In the earlier stages the two can be separated, leaving a velvety surface on the vein, but more commonly in attempts to separate vein from growth it is the growth that tears, which indicates that definite invasion of the outer muscular coat has already taken place. Coincidently with the progressive invasion of the muscular coat the growth creeps round the vessel, producing more or less constriction; but in some cases the muscular wall is destroyed before the vessel is surrounded completely. When the muscular coats have been perforated and lost in the new tissue masses form under the intima and cause soft warty projections into the lumen of the vessel. Sections of six such cases showed a dense mass of growth containing fibrous and elastic tissue, lined by intima. In no case was the intima perforated, though in one it was reduced in places to a single layer of cells. Carcinomata show a greater degree of local malignancy than sarcomata in this respect. In a section from a mediastinal carcinoma ulceration had taken place into the lumen, though the vessel was affected but little in other respects.

Clinically, the relation of the growth to the superior vena cava is very important. The vessel is the venous channel from the head and neck and upper part of the body, and the change for the worse when serious obstruction occurred was very striking in most of the last ten cases of the series. In nine of them the vein was attacked posteriorly, on account of its relation to the right peribronchial glands; in six of them the projections mentioned above were found, and it seems probable that they are the cause of venous obstruction whenever it is of sudden onset. The patient then rarely survives for more than three weeks.

Retardation of the venous flow results, as pointed out by Box and Eccles (13), in the opening out of a deep and, later, of a superficial collateral circulation. The former consists of two channels:

1. If the azygos vein is patent blood can find its way from the lumbar veins

which connect with the azygos into the lumbar, renal, and iliac tributaries of the inferior vena cava.

2. The innominate vein is connected with the external iliac by means of the superior and inferior epigastric veins.

The superficial veins of the chest are divided into mesial, lateral, and posterior groups.

1. The mesial veins on the upper part of the chest are drained by the anterior intercostal tributaries of the internal mammary veins, and those near the free margin of the chest by tributaries of the superior epigastric veins. Enlargement of these two sets of veins is often a prominent feature, and is important as an indication that the deep collateral channels are insufficient. An enlarged vein, the superficial superior epigastric, is often seen running from the ensiform cartilage to the umbilicus. It communicates above with the internal mammary veins and below with a plexus round the umbilicus. Blood from these three sets of veins finds its way by the superficial inferior epigastric, by tributaries of the deep inferior epigastric, and by branches of the lumbar veins, to the internal saphenous, external iliac, and inferior vena cava respectively.

2. The lateral superficial veins are part of the path from the axillary vein to the superficial inferior epigastric, through the external mammary and thoracico-epigastric veins.

3. The posterior lie between the intercostal veins above and the lumbar veins below.

Constriction of the superior vena cava will therefore cause dilatation of all of these superficial veins.

In some cases the azygos is involved as it arches over the glands round the right bronchus, or, less often, in the posterior mediastinum; this should result in dilatation of the lumbar veins and of the superficial veins on the lateral and posterior aspects of the thorax. Roberts (14) points out that oedema of the loins and of the abdominal wall is a symptom of obstruction of the azygos. There should be, theoretically, some congestion of the spinal cord.

Constriction of the right or left innominate veins causes very obvious dilatation of the vessels of the head and neck, and does not call for remark, except that unilateral dilatation is an aid to the localization of the growth.

The pulmonary veins are extensively diseased, especially in the substance of the lung. It is probable that they are the first veins to be penetrated, and are, therefore, responsible for metastases.

The inferior vena cava has only a short intrathoracic course, and is, in consequence, rarely affected. In Case 23, however, the posterior mediastinal mass was causing definite narrowing of the opening into the right auricle; in Case 24 it was reduced to a slit between two projecting masses of growth.

The arteries. The arterial wall is highly resistant to sarcomata. It is common to find an artery completely buried in a mass of growth, but not narrowed or invaded. The pulmonary artery and arteries such as the sub-

clavian are sometimes slightly narrowed or thrown into longitudinal folds, but even in such cases it is not difficult to tear the artery from the growth which surrounds it. No invasion was seen microscopically in the sections made from larger or smaller arteries.

A growth arising in the glands in front of the arch of the aorta and closely applied to it may give signs resembling those of aneurysm, and cause, for a time at any rate, considerable difficulty in diagnosis.

The heart. Ten of the twenty-six cases showed invasion of heart muscle. The upper and posterior surfaces of the auricles are invaded first, by direct downward extension of the mediastinal growth. In Case 23 it was found almost as low as the auriculo-ventricular groove. In two or three cases the posterior auricular wall was bulged forwards, and polypoid projections are occasionally seen. Case 24 presented the remarkable condition illustrated in Plate 10: no muscular tissue could be found at the bases of the masses projecting into the auricles.

Microscopically, columns of growth are seen spreading between the muscle fasciculi, and isolating the outlying portions which gradually degenerate. In three cases in which the muscle had suffered severely the inner layers of the endocardium were intact; in Case 24 it appeared to have been destroyed in some places, and in others reduced to a single layer of cells.

The effects on the heart are surprisingly small. In view of the fact that the upper part of the right auricle, which contains the centre for the initiation of the heart-beat, is the commonest site for malignant invasion, alteration of the rhythm and frequency of the pulse would be expected. No irregularity was noticed in Cases 17–26, and pulse-rates of 70 to 100 were the rule, with rises to 120 with the onset of terminal broncho-pneumonia. In Case 24 it varied between 110 and 120, though there could have been no conduction of impulse or stimulus in the posterior auricular walls. Unfortunately, no electro-cardiograms could be taken from these cases.

Displacement of the heart forward and to the left occurs especially with posterior mediastinal growths, and may help to confirm an erroneous diagnosis of fluid in the right pleural sac. Steell (15) reports a sign produced by the displacement of the heart. In cases of posterior mediastinal growths he noticed that the heart appears to thrust itself forward *en masse*, so that a greatly exaggerated pulsation is seen, universally distributed over the cardiac region. In Cases 22 and 23, in which large posterior mediastinal masses were found at the autopsy, the sign had not been noticed in the wards.

The pericardium. Nineteen of the twenty-six cases showed invasion of the pericardium, which may take one of several forms.

The upper and posterior parts are often in contact with growth which adheres to the parietal layer, and slowly invades it, so that it is not uncommon to find the lower part of the mediastinal growth covered by a granular mottled layer of thickened pericardium. In such cases there is rarely ulceration of the pericardial surface.

Later, warty or polypoid projections into the pericardial cavity are formed, as in Case 24, but the serous lining was found to be intact in all of the six cases in which they were present.

In a third form there is thickening of the visceral pericardium. The auricular portion is affected more often than the ventricular. In Case 19 the thickening had gone on to the formation of nodules in the ventricular epicardial layer.

Pericardial friction, though not heard in any of the twenty-six cases, is occasionally present. According to Roberts (14) its presence in older patients is a point strongly in favour of malignancy.

The nerves. The larger nerves show a considerable degree of resistance. It is often possible to trace a nerve for some distance through a growth, but, when deeply embedded, the nerve is generally constricted or flattened.

Sections show that invasion does not begin before the nerve has been completely surrounded. Growth then creeps between and separates the bundles of fibres, but is slow to invade the bundles themselves and destroy the fibres. It is therefore possible that a nerve which has become untraceable to the naked eye in growth is still functional. Clinical evidence, however, is rather against this supposition. Many of the symptoms of the disease, some of them occurring early, are attributable to irritation or paralysis of the different intrathoracic nerves, especially the recurrent laryngeal, the vagus, the phrenic, and the sympathetic.

The lymphatic glands. Early infiltration of a gland is often more easily detected macroscopically than microscopically, unless the sarcoma contains some characteristic cell such as the spindle cell.

The gland capsule, which offers considerable resistance to the malignant process, is pierced sooner or later, and growth invades the surrounding connective tissue. Extension also takes place by means of the glandular lymphatics, especially the afferent. In this way the pulmonary glands are invaded from the bronchial and the chain of cervical glands from a mass at the root of the neck.

The matting together of enlarged glands gives rise to symptoms of mediastinal pressure, and it will be well to consider how far symptoms caused by such masses of glands can help in the estimation of the anatomical relations of the tumour.

The *superior* mediastinum contains important groups of glands in front of the arch of the aorta, round the arteries springing from it, and round the innominate veins. Growth in these glands may give rise to a tumour sufficiently large to be felt at the base of the neck, or to a chain of enlarged glands accompanying the jugular vein. Growths not large enough to appear in the neck may cause signs of pressure: oedema of the larynx, oedema and venous dilatation of one or of both sides of the neck and head, compression of the trachea, unilateral or bilateral paralysis of the vocal cords, paralysis of the cervical

sympathetic, and pressure on the brachial plexus. The most important of the physical signs are dullness over the manubrium and a systolic bruit.

A growth pushing forward into the *anterior* mediastinum generally gives rise to a sense of constriction. It causes more or less retraction of the lungs, and gives a large central area of dullness, over which the heart sounds are plainly heard.

Posterior mediastinal growths involve the glands related to the oesophagus, and it is, in consequence, not uncommon to find either irritation spasm or constriction, as evidenced by means of the X-rays or by a history of dysphagia. It would seem that, from the cases studied, sarcomata which originate in the posterior mediastinal glands attack especially the right lung. As mentioned above, cardiac displacement and the sign discovered by Steell are suggestive of a posterior mediastinal growth.

The *middle* mediastinum contains, however, the most important groups of glands:

1. The intertracheo-bronchial, or *bifurcation* glands;
2. The prae-tracheo-bronchial, or *peribronchial* glands;
3. Some of the interbronchial, or *pulmonary* glands.

The topography of these three groups was minutely studied by Barety (17) in his classical description published in 1874.

The right peribronchial glands are related, in front, to the superior vena cava; internally, to the trachea; behind, to the right vagus nerve; externally, to the mediastinal surface of the right lung; below, to the right bronchus and to the pulmonary artery; while their upward extension is related to the azygos vein, to the subclavian arch, to the right recurrent laryngeal nerve, and to the lower end of the jugular trunk. They lie, moreover, on the lymphatic path from the right lung. It is therefore very important to search for signs of disease in the region of the right bronchus, and, if they are present, to discover which of these structures is involved. In the majority of cases signs of invasion of the right lung indicate that the right bronchial glands are affected as well. The left peribronchial glands are not so numerous, and are not so important because they are not related to a vein corresponding to the superior vena cava.

The bifurcation glands are close to the upper border of the heart, and receive most of the lymphatic vessels from it.

The pulmonary glands are found in the angles formed by the first to the fourth divisions of the bronchi; they are almost surrounded by lung tissue, and receive especially the perivascular lymphatics (Poirier and Charpy).

The oesophagus. The oesophagus is affected chiefly by posterior mediastinal growths, and especially in the upper part of this space. It is stretched over a mass of enlarged glands, displaced to one side, or actually invaded, as in ten of the twenty-six cases.

The outer coat early becomes adherent: piercing the middle coat as well the growth then tends to spread between the middle and inner coats in the plane of the chief lymphatic network, causing more or less constriction of the lumen.

Sarcomata rarely pierce the inner coat to attack the mucous membrane, whereas carcinomata do so, though the muscular coats may be affected comparatively slightly.

A history of difficulty in swallowing is not often obtained, but slight constriction or spasm from the irritation caused by commencing invasion or paresis from involvement of the vagus are probably relatively common. They can be detected by X-ray examination when quite unsuspected clinically.

The thyroid gland. Superior mediastinal tumours, from their position, are the most likely tumours to attack the thyroid gland, but it is stated that this rarely occurs. Case 21, however, showed it. The gland was pale, and continuous below with the growth round the innominate vein. Microscopically, the gland was much degenerated, and columns of growth could be seen running in the connective tissue framework. Invasion of the gland was also seen in a case of carcinoma.

The bones. Steven stated that in his experience mediastinal sarcomata never invade bone, and Roberts (16) agrees with him. In Case 1 a small area of the sternum was said to be eroded. In this respect sarcomata differ from carcinomata.

Extrathoracic Secondary Deposits.

The secondary deposits in the liver are often in the upper part of the organ, and possibly reach it by backward extension from the diaphragmatic lymphatics. When, however, growth has ulcerated into a vein, deposits may occur in any part of the liver, as well as in brain, spleen, kidneys, suprarenals, intestines, &c. The pancreas is invaded as a rule from the aortic group of glands, which are closely connected to the receptaculum chyli, and perhaps the latter is also the path by which the suprarenal glands are invaded.

Diagnosis.

There can be little doubt that many cases of mediastinal sarcoma pass unrecognized. In those especially in which dyspnoea is an outstanding feature should the possibility of the presence of a new growth be remembered.

In examining a suspicious case it is necessary to decide on the presence or absence of signs and symptoms of—

1. Mediastinal pressure;
2. Involvement of lung;
3. Secondary deposits.

1. *Mediastinal pressure.* The effects of the pressure caused by a new growth in the different parts of the mediastinum have been dealt with in the consideration of the different intrathoracic structures which may be affected. Some of these effects can be produced by aneurysm, by non-malignant mediastinal growths, by glandular enlargements, by cysts, and by acute and chronic

mediastinitis; of which, judging by the literature of the subject, aneurysm is by far the most important. The signs of an aneurysm of the arch of the aorta and of a growth in the same region may be precisely similar, except that inequality of the radial pulses is, perhaps, less marked in the latter. In such cases collateral evidence, such as the age and sex of the patient and the presence or absence of a history of syphilis, is of value, and the progress of the case sooner or later clears up any doubts.

2. *Involvement of lung.* Those cases of primary mediastinal sarcoma in which the mediastinal growth is in a silent area and the pulmonary growth is spreading outwards along the bronchial tree may give a clinical picture closely resembling that of pulmonary tuberculosis. A history of cough, expectoration, staining of sputum, night-sweats, shortness of breath, and wasting, combined with impairment of note and bronchial breath sounds at the apex of one lung, though almost conclusive of pulmonary tuberculosis, may very well be due to the rarer affection, sarcoma. The points which would be strongly in favour of the latter are absence of pyrexia, persistent absence of tubercle bacilli from the sputum, and paroxysmal attacks of dyspnoea, while the occurrence of signs of mediastinal pressure in such a case would settle the diagnosis. It is important to remember that pulmonary tuberculosis is, roughly speaking, a bilateral, and sarcoma a unilateral, disease. Pulmonary tuberculosis, judging by the Victoria Park series of cases, is much more commonly confused with mediastinal sarcoma than is aneurysm. At least six of the last ten cases of the series were sent to the hospital with a diagnosis of tuberculosis.

For some cases which present only pulmonary symptoms, fibrosis of lung with thickening of the pleura, bronchiectasis, or abscess of lung may be a more reasonable diagnosis than new growth. Case 20, for instance, was at first diagnosed as the former, while the reverse was seen in a more recent case in which new growth was suspected, but which proved to be a pulmonary fibrosis.

1 and 2. *Mediastinal pressure and involvement of lung.* The combination of signs of mediastinal pressure and of pulmonary involvement is almost diagnostic of new growth. There are, no doubt, many possible conditions which would give rise to signs of disease in both places. Pulmonary tuberculosis with much enlarged bronchial glands, syphilitic fibrosis of lung with mediastinal gumma, hydatid disease, and combinations of lung disease and of non-malignant mediastinal tumour are possibilities rather than probabilities. It is in such cases that an intimate knowledge of the pathological anatomy of mediastinal sarcoma is of the greatest value.

3. *Secondary deposits.* Secondary nodules in the skin or tumours in the abdominal viscera form, in some cases, useful evidence, but it cannot always be proved that the intrathoracic and extrathoracic tumours are interrelated.

X-ray examination is, in the earlier stages of the disease, rather fallacious. In two of the last ten cases experienced radiographers had confirmed by X-rays an erroneous diagnosis of pulmonary tuberculosis. In two other cases shadows said to be due to growth were seen in the 'unaffected' lung, but a careful search

at the post-mortem several weeks later revealed no growth on that side. In the later stages bulging of the mediastinal shadow and opacity of one lung may leave little room for doubt, but such cases should have been correctly diagnosed on clinical grounds with a considerable degree of certainty. The X-rays are, however, very valuable in detecting early compression or spasm of the oesophagus, unrecognizable by other means; and in the differentiation of cardiac displacement due to pleural effusion from that due to mediastinal tumour.

Examination with the laryngoscope should be performed in every case. Early abductor paralysis may be noticed before any alteration has occurred in the voice. Compression of the trachea or oedema of the larynx may be seen in less early cases.

The cases in which there is a pleural effusion are not uncommon, and present some difficulty in diagnosis. The effusion is by no means always haemorrhagic, and, further, blood found on exploration does not necessarily mean a haemorrhagic effusion. Careful exploration in an area over which there are signs of effusion may fail to find fluid. The possibility of new growth should be remembered in all such cases. The 'silence' gives place later, and often rather suddenly, to signs of consolidation.

In the differential diagnosis from intrathoracic carcinoma a careful search must be made for a primary focus elsewhere, for carcinoma in the chest is more often secondary than primary. Of the latter epithelioma of the oesophagus is the commonest form.

It is often possible to diagnose with a considerable degree of accuracy the relations of a mediastinal tumour and to anticipate to a certain extent future symptoms. The evidence for the presence of growth in different parts of the mediastinum must be carefully collected, and a mental picture of the tumour formed. A silent area, in which a tumour gives rise to no symptoms, existing between places at which there is evidence of pressure, may be supposed to be occupied by growth. When a tumour, known to be present in the region of the right bronchus, begins to produce signs of compression of the superior vena cava, it is unlikely that the patient will live for more than a few weeks.

Conclusions.

Primary sarcoma of the mediastinum is by no means a very rare disease. Originating either in one of the groups of mediastinal lymphatic glands or occasionally in the thymus gland, the new growth enlarges, by invading surrounding connective tissue and by spreading to neighbouring glands, to form a mass, often of considerable size, which involves to a greater or less extent almost all of the structures of the thorax.

The term 'lymphosarcoma' is convenient as expressing the origin of the growth, but does not properly indicate its microscopical characteristics, which differ from those of lymphatic tissue.

Though proliferative rather than destructive the growth exhibits a local malignancy, especially on lung tissue, and on the walls of the air passages and of the veins.

After reaching the pulmonary glands it either spreads rapidly along the bronchial tree to the pleura, forming deposits beneath it and in the neighbourhood of bronchioles about an inch from the surface, before general infiltration of the lung commences; or invades the lung directly, destroying and replacing lung tissue from the root outwards. The first process—the 'diffuse'—is associated with pleural effusion, with bronchiectasis and purulent bronchitis, with the presence of infiltrated cervical glands, and with the formation of secondary metastatic deposits. The second—the 'central'—rarely shows these characteristics, and is a more chronic process.

The relation of the mediastinal tumour to the superior vena cava is very important, the onset of serious obstruction of this vessel, as evidenced by the opening out of a deep and later of a superficial collateral circulation and by oedema, being followed by a rapid deterioration in the patient's condition.

The growth rarely penetrates the intima of the larger veins, the serous lining of the pericardium, the endocardium, or the mucous membrane of the oesophagus.

Though the signs produced may resemble those of many other complaints, it is often possible to form a correct diagnosis of the presence and relations of the tumour. If the different signs can be interpreted as evidence of the local presence of new growth a composite deduction of its extent may be made with the help of an intimate knowledge of the pathological anatomy of the disease.

Cases of primary mediastinal sarcoma are often wrongly diagnosed as pulmonary tuberculosis, and occasionally as aortic aneurysm or as pulmonary fibrosis.

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DESCRIPTION OF PLATES.

PLATE 9. *A section through the right lung of Case 26, showing growth of the diffuse type in different stages:—consolidation of the lower part, and infiltration of the upper part, of the lower lobe, and early invasion (together with arrested tuberculosis) of the upper lobe. The appearance of the middle lobe, which is anterior to the plane of the section, resembled that of the lower lobe. A portion of the central mediastinal mass appears below the bifurcation of the primary bronchus.*

The growth is oldest at the base, where it is lobular. A fibrous framework containing vessels and bronchioles separates the lobules, most of which show central degeneration. It could not be ascertained whether the growth had commenced in the centre or at the periphery of the lobules. In the upper part of the lower lobe the growth is denser, and therefore probably older, beneath the pleura and at rather more than an inch from the surface than elsewhere. Microscopically, the infiltration of the less affected parts was greater than appears to the naked eye. The bronchi of the lower lobe are thickened and slightly dilated, the bronchioles dilated and filled with purulent débris. The pulmonary glands are enlarged and partially invaded.

At the apex of the lung are several subpleural deposits, one particularly dense, and a few scattered deposits elsewhere in the upper lobe. Malignant invasion of the perivascular lymphatics was not as well marked as in other cases. Chiefly about an inch below the pleura are numerous fibrous masses, containing areas of round-celled infiltration. Most of them are definitely related to the wall of a bronchiole. They appear to be fibrous tubercles, without central caseation or giant cells, and in one a tubercle bacillus was discovered. On the mediastinal aspect of the upper lobe there is a diffuse broncho-pneumonic condition.

The left lung showed typical tubercles in the lower lobe, and in the upper lobe small areas of infiltration with polymorphonuclear leucocytes. They had the distribution of early malignant deposits, but microscopically resembled early tuberculous rather than malignant lesions. Tubercle bacilli were found only in the tubercles.

PLATE 10. *A dissection of the thoracic contents of Case 24 to show 'central' growth in the right lung, and the relation of the mediastinal growth to the trachea, pulmonary artery, pericardium, and auricles.*

The growth is invading the lung from the root, and also directly from the main mass of growth in the posterior mediastinum through the pleura below the root. It is sharply outlined, and the remains of pulmonary glands are visible. Most of the bronchi in the growth are plugged by malignant débris and invisible. The upper lobe is compressed and congested, with an area of haemorrhage in the lower part.

The middle lobe shows an area of commencing infiltration of the diffuse type, the lower lobe a more advanced but similar condition.

The inner surface of the pericardium is granular, and mottled by small veins. Some projections of growth into the pericardial cavity are seen behind the upper part of the right auricle. The posterior auricular walls are replaced by growth which has fungated forwards into each auricle, so that the inferior vena cava has only a narrow opening on the surface of one of these masses.

The central mediastinal mass reaches up to the bifurcation of the trachea, but the greater part is in the posterior mediastinum and invisible.

No growth was found in the left lung.

PLATE 11, FIG. 1. Part of a section from a case of the diffuse type of growth, showing the pleura, part of a subpleural deposit, and perivascular growth.

The pleura is apparently unaffected. The subpleural growth is dense, and contains a fibrous network and numerous dilated venules. Parts of the lung parenchyma immediately adjacent to this deposit are quite free from growth. No bronchioles are seen in the figure, but two arteries are shown surrounded by growth, as were almost all of the arteries in the parts of the section not illustrated.

FIG. 2. Part of a section from the growing edge from a case of the central type of growth.

The alveoli are filled with 'catarrhal' cells. Growth is spreading downwards, primarily in the alveolar walls. Near the top can be seen part of the fibrous band which elsewhere in the section formed a sharp boundary line between growth and uninvaded lung.



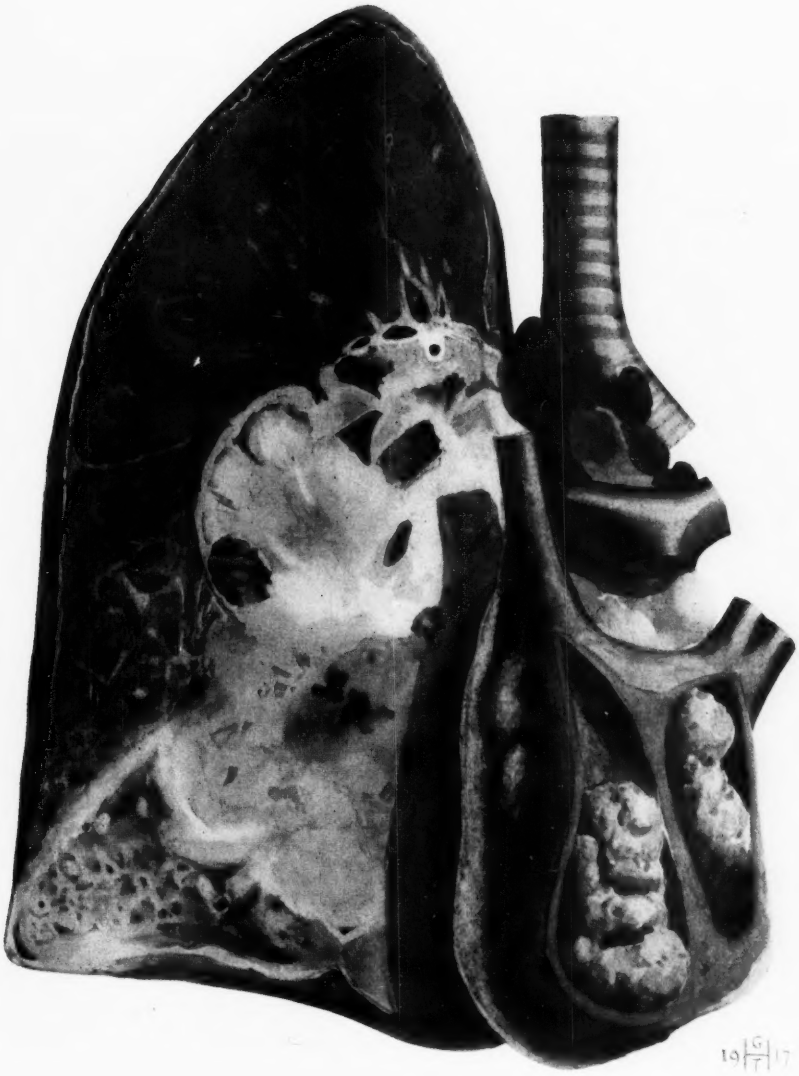




FIG. 1.

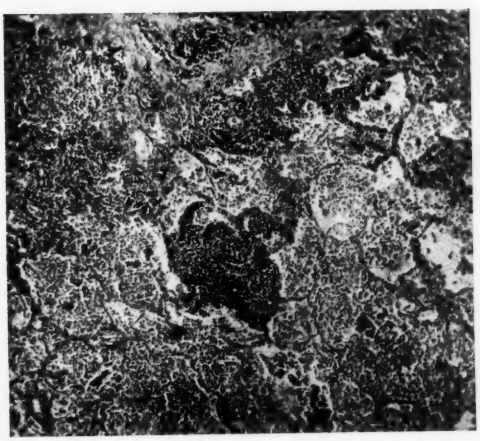


FIG. 2.

×40



ON THE PATHOGENESIS OF DIPHTHERITIC PARALYSIS

By F. M. R. WALSHE

Introduction.

Of the acute specific fevers in which nervous complications arise diphtheria is that most definitely associated with a clearly defined nervous system-complex.

Post-diphtheritic paralysis in man presents a clinical picture of remarkable constancy, and both its pathological and clinical aspects have been extensively studied. In this country, particularly, much light has been thrown on its pathology by the reseaches of Sidney Martin, Charles Bolton, Rainy, and many others, while innumerable observers have so defined its clinical features that it would seem that little remained to be said.

Nevertheless there are still gaps in our knowledge of the subject, and nowhere is this more apparent than when we come to consider the path and manner of infection of the nervous system by the toxin of diphtheria. Nothing definite appears to be known of this, and, with few exceptions, an extensive literature does not even indicate the existence of this problem.

Writing in 1909, Guillain and Laroche (9), in a paper on the pathological physiology of diphtheritic paralysis, held that 'paralyses in diphtheria were, in the majority of cases, related to the seat of formation of the toxin, and that the nerve centres were attacked by a process of ascending toxic neuritis, similar to the toxic neuritis in tetanus and hydrophobia', and further that 'morbid anatomy had not afforded any precise evidence as to the pathogenesis of paralysis in diphtheria'.

Previously, however, in 1904, Babonneix (1) had noted the remarkable relationship existing between the primary diphtheritic lesion and the subsequent paralysis. This, his experiments led him to conclude, was due to an ascending toxic infection along the peripheral nerves to the nervous centres. He considered therefore that as regards its pathogenesis diphtheritic paralysis was comparable with rabies and tetanus.

Rabies and tetanus have long been recognized as toxaemias ascending the nerves. Indeed, the phenomena of 'local tetanus' and the spread and generalization of the tetanic spasms from the region of the infective lesion made it impossible to escape the inference that the path of infection of the central nervous system was along the nerves.

The whole question of infection along nerve trunks has been made the

[Q. J. M., April, 1918.]

subject of numerous investigations. These have established the existence of an ascending perineural lymph stream and the infection of the central nervous system by organisms and toxins along this path.[1]

In view of the frequency of diphtheritic paralysis and the extent to which it has been studied it is remarkable that the views quoted above have not obtained wider acceptance and notice.

The tendency, too, of clinical writers has been to regard the whole picture as one mysteriously peculiar to diphtheritic toxaemia; while the fact that it is at once the only clinical type of polyneuritis characterized by profound and extensive cranial nerve palsies, and the only one definitely due to an infective focus which is exclusively limited to a small region of the body innervated by the cranial nerves that are most involved, has not received the attention its significance merits.

It is important, therefore, to reconsider the pathogenesis of diphtheritic paralysis, and to examine the evidence in favour of the hypothesis that it is a toxaemia of the nervous system ascending the nerves innervating the infective focus by their lymph channels.

'Lymphogenous' Infections of the Central Nervous System and the Pathology of the Nervous System in Diphtheria.

The suggestive work of Orr and Rows (13) on lymphogenous infections of the central nervous system is of the greatest importance in this connexion.

The result of a prolonged series of investigations by these authors has been to confirm the existence of an ascending lymph stream in the perineural sheath of nerves. Toxins and organisms reach the central nervous system by this path and spread in the lymph spaces of the pia arachnoid and in those in the substance of the cord. Here they give rise to an inflammatory reaction in the connective tissue elements of the cord, to chromatolysis in the nerve cells, and to myelin degeneration in the spinal roots. These changes occur in those segments of the central nervous system bearing anatomical relationship to the nerve supply of the infective focus. The nerves from this focus show an ascending perineuritis spreading to the cord by the spinal ganglia and spinal roots. It is noteworthy, in view of negative findings in the nerves in some cases of diphtheritic paralysis, that the myelin degeneration occurs almost exclusively in the intramedullary course of the nerves, i.e. from the point where the neurilemma sheath is lost.

Hence it has been assumed that either the presence of the neurilemma sheath, or, more probably, the peripheral situation of the lymph channels, protects the myelin sheaths in the peripheral course of the nerves.

It is not necessary here to discuss the nature of the inflammatory reaction

[1] It may be noted that an interesting complement to these researches is afforded by Sherrington's observations on the development of strychnine poisoning and its effects on reflex action.

occurring in the fixed connective tissue cells and in the adventitial sheaths of the veins in these infections.

In a series of cases of suppuration in the limbs, trunk, and head, Orr and Rows have found an ascending lymph infection of the corresponding nerves giving rise, as described above, to meningomyelitic changes in the central nervous system.

Experimental observations in which gelatin capsules containing cultures of organisms were placed against the sciatic nerve, the spinal dura mater, and in the substance of the cheek in animals gave results identical with those obtained from the clinical cases.

Independently, Babonneix (1, 2) arrived at similar conclusions regarding diphtheritic paralysis, as a result of experimental work. By injections of diphtheria toxin subcutaneously into animals he was able to produce local paralysis and acute ascending paralysis of Landry type.

He noted a remarkable anatomical relationship between the primary inoculation lesion and the paralysis.

Following injections into the sciatic nerve he found, associated with a local paralysis, an 'ascending neuritis' and pathological changes in the lumbar cord; chromatolysis and myelin degeneration in the spinal root fibres. He drew the conclusion that the paralysis in diphtheria followed an ascending neuritis and secondary involvement of the central nervous system.

Oppenheim's (12) views are less clearly formulated, though somewhat similar. He says 'the toxin first acts on the nerves in the immediate vicinity of the infective focus; it then passes into the laryngeal and oculo-motor nerves and finally becomes still further disseminated'. Unfortunately general statements of this type do not help to solve the essential problem of how and by what channels this dissemination occurs, and it is clear that the writer has no definite conception of the pathology of the process.

Oppenheim and most other authors describe a local and a generalized paralysis in diphtheria, referring thus to the cranial and the spinal nerve affections respectively. But if we accept the view of Babonneix that the primary lesion is an ascending neuritis, it is clear that even if we allow such a subdivision of the condition, the differentiation must not be between spinal and cranial nerve symptoms, but between paralyses resulting from lesions of the nerves innervating the infective focus and those due to lesions of nerves secondarily, or at least otherwise, involved. In this second class we should have to include the oculo-motor with the spinal nerves, for the third nerves bear no anatomical relationship to the local lesion on the tonsils, and we cannot speak of an ascending neuritis in connexion with it or with the spinal nerves. This preliminary consideration will serve to give us an idea of the complexity of the pathological process with which we are dealing.

The investigations of Babonneix and the views of Guillain and Laroche alone show any evidence of a definite conception of a complete pathology of the

condition, while for the rest the literature consists of histological and experimental observations in no way correlated and often conflicting in their results, so that it seems hopeless to expect enlightenment from them.

Indeed in a review of the literature in 1900, Rainy (14) draws attention to the numerous divergences of opinion among authors as to the essential pathological lesion. And at first sight it is difficult to account for the lack of agreement as to actual pathological structural changes in a disease so common and so extensively studied. Further work since this review has done nothing to lessen the confusion which renders this chapter of pathology so inconclusive.

Several factors have probably gone to produce this state of affairs. Among these is an omission on the part of observers to discriminate between the pathology of human and experimental diphtheria. When we take into account the very different circumstances of the infection in each case it may be readily conceived that the character of the paralysis and the nature and distribution of the morbid changes in the nervous system may differ, and to compare without qualification the form of the paralysis and the nervous lesion following faucial diphtheria with those following the intravenous injection of diphtheria toxin into a guinea-pig is to court error and confusion.

For a toxin reaching a restricted part of the central nervous system by the lymph channels of certain cranial nerves may surely be expected to produce a different picture clinically and pathologically from that produced when it reaches the nervous system by the blood stream after intravenous injection.

A further possible source of error lies in the fact that with regard to fatal cases of diphtheria in man in many instances the pathological findings have not been strictly correlated with the clinical phenomena during life. It is difficult to appreciate the significance of pathological changes unless the character and distribution of the nervous symptomatology are known. For example, a case dying early in the stage of cranial nerve palsy may give different pathological findings from one examined at a stage when multiple neuritis has supervened and the bulbar symptoms have abated. This is especially so, also, when an observer draws deductions as to the whole pathology of diphtheritic paralysis from an examination of the phrenic nerves and the cervical segments of the cord from which it arises; while another draws equally far-reaching conclusions from examination confined to the medulla and cranial nerves in cases of which no adequate clinical details are available.

It is not surprising, therefore, that no agreement has been reached as to the essential nervous lesion in diphtheritic toxaemia.

It is possible, too, that the histological methods employed have been directed primarily to detect abnormalities in nerve cells and nerve fibres, without due regard to the fixed connective tissue cells of the central nervous system and its vascular and lymph structures. The importance of studying these in inflammatory and degenerative conditions of the nervous system, if a comprehensive and complete picture of the pathology of any infection or

intoxication is to be obtained, is known to every neuropathologist and is well exemplified in the work of Orr and Rows.

From what has been said already in connexion with the views expressed by Babonneix and Oppenheim and from these observations, it will be seen that the underlying factor in all these possible causes of error is that these numerous researches have not been guided by any clear conception of the pathology of the process by which the nervous system becomes involved.

A Comparative Analysis of Human and Experimental Diphtheria with reference to the Nervous System: the Local Lesion, the Symptomatology, the Pathological Changes.

It is therefore important with this hypothesis, in view in comparing diphtheritic paralysis in man with that produced experimentally, to correlate the seat and nature of the local lesion with the topography of the paralysis and that of the morbid changes in the nervous system.

If we do this we find at once a striking parallelism between clinical and experimental diphtheria of the nervous system, and in both instances strong evidence in favour of a lymphogenous infection by the peripheral nerves.

I. *Human Diphtheria.* (a) *The local lesion.* With the exception of rare cases of wound and cutaneous diphtheria, which will be considered later, the infective focus in the disease in man is constantly situated on the tonsils and fauces, occasionally in the nose and larynx. This extremely circumscribed lesion is innervated by the fifth, ninth, tenth, and eleventh cranial nerves. It is not necessary to go into the anatomical minutiae of this innervation. The characteristics of the local lesion resemble very closely those of the capsules of organisms used in the experimental observations of Orr and Rows, from which only toxins diffuse around the nerve.

(b) *The symptomatology.* Diphtheritic paralysis in man is ushered in by an extensive cranial nerve palsy,[2] frequently followed in two or three weeks' time by what is clinically a multiple neuritis.

This evolution and course are characteristic of the paralysis due to diphtheria, and in no other clinical form of polyneuritis is there a cranial nerve involvement at all comparable with the one in the condition under discussion.

It is scarcely necessary here to discuss in detail the symptomatology of diphtheritic paralysis. With regard to the cranial nerve involvement, however, certain considerations are important. It has been noted that of the nerves concerned those innervating the tonsils and fauces are earliest and most severely affected. It has also been pointed out that the third nerve, which very commonly shows involvement, does not bear any anatomical relation to the local lesion.

[2] It may be noted that, compared with spinal nerves, these have a relatively short course from the infective focus to their nuclei in the brain stem, and, as Orr and Rows have shown, this is associated in cases of lymphogenous infections with relatively more intense reaction in the central nervous system.

This fact will come under consideration later. The spinal accessory nerve is not often described as in any way affected, but there is frequently to be observed a profound weakness and tenderness to pressure of both sterno-mastoids during the first stages of diphtheritic paralysis, and this may, in all probability, be considered as of the same nature as the other cranial nerve palsies.

It may be stated, therefore, that there is a close anatomical relationship between the nerve supply of the infective focus and the incidence of the paralysis in its initial and most characteristic stage.

(c) *The pathological changes.* In fatal cases of diphtheria Bolton (3) found acute degenerative changes in the medulla; marked chromatolysis in the vagal nuclei, involving the whole cell body and even associated with changes in the cell processes. The vagus nerve he found intact. Whether the degenerative changes noted in the cell processes may be taken to indicate myelin degeneration in the intramedullary course of the vagus is not certain, but negative findings in the peripheral course of the nerve have, as has been shown in parallel conditions, no significance (13).

The balance of evidence goes to show that in man the medullary nuclei constantly show changes. Of spinal cord changes it is difficult to make any statement on which there is wide agreement, and this perhaps is reasonable evidence of their inconstancy.

On the whole, then, there is a correspondence between the seat of toxin formation and the incidence of the morbid changes in the nervous system.

II. *Experimental Diphtheria.* (a) *The local lesion.* A similar analysis of experimental diphtheritic paralysis affords parallel results.

The local lesion is usually a subcutaneous injection into a limb, or less commonly intravenous injections of a selected toxin. The former is not strictly, and the latter is in no way, comparable with the faucial lesion of clinical diphtheria.

With intravenous injections there is no true local lesion, but a blood infection, and this will be considered later.

(b) *The symptomatology.* It is interesting to record the nature of distribution of experimental diphtheritic paralysis in view of these facts.

Ransom (15), inoculating the hind limbs of guinea-pigs subcutaneously, records that there are no bulbar symptoms; but the paralysis begins locally in the injected limb and becomes generalized, involving the neck and abdominal muscles, but especially those of the hind limbs.

Dean (7) says that, after subcutaneous injections of toxin, paralysis sets in from the fifteenth to the thirtieth days. 'The hind limbs are usually first attacked, though sometimes the first signs are apparent in the fore limbs. When the hind limbs are first attacked the paralysis may ascend and affect the trunk and fore limbs.'

Crocq (6) states that 'Diphtheritic paralysis is distinctly different in man and in the rabbit. In the former it generally begins with involvement of the palate and throat, in the rabbit by weakness of the hind limbs. In man

diphtheria seems to produce two different kinds of paralysis, in which the one remains localized in the mouth, eyes, nose, larynx, and pharynx, while the other is generalized and may affect the whole body, beginning with the lower limbs.'

In the same way Bolton (3) says: 'It is to be noted that in man muscular paresis in diphtheria most commonly affects the muscles supplied by the cranial nerves, whereas in the rabbit it chiefly affects those supplied by the spinal nerves. It seems therefore that in the higher mammals the poison especially attacks the medullary centres and the cranial nerves, and in the lower mammals the spinal centres and spinal nerves.'

The conclusions of Babonneix (2) have already been considered.

(c) *The pathological changes.* If we now examine the morbid anatomy of the nervous system we find the same relationships.

Bolton and Bown (4), giving intravenous injections of toxin to rabbits and monkeys, produced chromatolysis in spinal, medullary, pontine, and mesencephalic cells.

In rabbits the lower part of the cord was most involved, the medulla being less affected in them than in monkeys. They found no definite focus of degeneration and record that the vessels in the nervous system were unaffected. They conclude that 'the diphtheria poison directly causes acute degeneration of certain cells of the central nervous system, and that these changes are not secondary to any changes in the circulation, and that the poison directly affects the peripheral nerves'.

Dudgeon (8) found no abnormal changes in the medulla in animals; while Crocq (6) states that in rabbits, 'In the cord the diphtheria poison produces very marked alterations of the grey matter, the cells become swollen, they stain badly, their nucleus and processes disappear; the neuroglia and ependyma proliferate . . . the white substance is but rarely affected. In the peripheral nerves a degeneration is produced. With regard to the medulla, slight cell degeneration at its lower part, its middle and upper parts remaining normal. The cranial nerves are not affected by the poison and a primary myelitis and a secondary peripheral neuritis are produced.'

Rainy (14) and Mouravieff (11) completely confirm all these observations, which accord with those of Babonneix (1, 2).

From this analysis the following points have become clear:

1. That in both human and experimental diphtheria, the evolution and topography of the paralysis and the incidence of the morbid changes in the central nervous system are closely related to the innervation of the infective focus. When, in experimental investigation, intravenous injections have been used we find generalized paralysis from the outset and widespread changes in cord and brain stem.

2. The apparent differences between the symptoms and morbid anatomy of diphtheritic paralysis in man and in animals respectively have a simple mechanical explanation and depend on the seat of toxin formation, and do not

demand for their explanation any speculations as to selective action of the toxin on medullary centres in man on the one hand and spinal centres in animals on the other.

Paralysis in Wound and Cutaneous Diphtheria: the Absence of Cranial Nerve Involvement: Illustrative Cases.

We have already therefore considerable evidence for the belief that in man diphtheritic toxaemia of the nervous system is primarily an ascending infection such as Orr and Rows have demonstrated to occur in infective foci of various types.

If we could bring forward definite cases of wound or cutaneous diphtheria followed by paralyses which showed in their evolution and topography evidence of 'local sign', i.e. were related to the seat of toxin formation in the matter of its innervation, we should, even in the absence of complete post-mortem confirmation, go far to prove the hypothesis.

The records of 'wound diphtheria' are from this point of view very disappointing and may be searched almost in vain for any record of nervous symptoms. Oppenheim (12) indeed briefly mentions two cases of interest in this connexion. In the absence of all details it is perhaps unprofitable to discuss them, but they have a definite bearing on the point at issue and should be recorded. He says: (1) 'I have also, in a case of a wound in the forearm infected with diphtheria, seen paralysis of accommodation appear before the paralysis became generalized'; and (2) 'That the diphtheritic toxin has first a local effect upon the nervous system is shown by a case in which the paralysis remained limited to the abdominal muscles after diphtheritic inflammation of the umbilicus in a new-born child. Accommodation paralysis may, however, be the first result of an intestinal diphtheria.'

It is not easy to draw any conclusions from these observations.

The same is true of cutaneous diphtheria, but the only case in which I have found paralytic phenomena recorded falls into line with the views here expressed. The case is described by Bolton and Brewer (5) as follows:

Case I. The patient, a young girl, came first under observation on September 29, 1903, with a sore in the left iliac region and upper part of the thigh, three by two inches in area, and of seven days' duration. It had apparently appeared spontaneously. The lesion yielded typical diphtheria bacilli in pure culture.

On October 5 profuse vomiting and albuminuria first appeared.

On October 28 the child's general condition was bad, but there was no obvious palsy.

On November 1 the patient was observed to be absolutely helpless and unable to move her legs; the upper limbs could be slightly moved. The muscles were flaccid and wasted and the knee-jerks absent. She could swallow, but intercostal and diaphragmatic paralysis was present and she died the same day—the 41st of the illness.

Pathological examination revealed a practically normal cord and medulla. Vagus, phrenic, and intercostal nerves were all normal. The anterior crural

nerve showed an early stage of myelin degeneration. The changes present in other elements in the central nervous system are unfortunately not recorded.

This is an example of a diphtheritic lesion of the skin followed by a severe and apparently ascending flaccid palsy, not associated with any cranial nerve symptoms.

The only definite pathological change recorded in the nervous system is an early myelin degeneration in a nerve definitely associated with the region of infection. Too much stress cannot be laid on this, but the significance of the clinical picture is clear.

Even more significant are the two cases of wound diphtheria now recorded, which have come under my own observation, and which may reasonably be considered to complete the clinical proof.

Case II. Post-diphtheritic paralysis, first appearing in the right hand and becoming generalized in the spinal nerves and presenting the picture of a multiple neuritis. The condition followed an infected wound of the right thumb received while performing tracheotomy on a fatal case of laryngeal diphtheria. No cranial nerve symptoms.

On April 19 Capt. E. J. B. performed tracheotomy on a patient with laryngeal diphtheria. He was not aware of cutting himself, but next morning noticed a painful bleb on the dorsum of the first phalanx of the right thumb. Later this broke down, leaving a sore raw surface, which spread rapidly and became covered by a greyish-yellow slough.

On April 23 he felt ill and shivery, and there was a marked lymphangitis up the arm and swelling of axillary glands.

On April 27 the diphtheria bacillus was isolated from the wound in pure culture and he was admitted to hospital. Antitoxin was given.

On April 30 marked symptoms of toxaemia developed, and during the following ten days albuminuria, periodical vomiting, and cardiac disturbance were present. The knee-jerks were brisk. Subsequently he improved and early in June was sent to a convalescent home. The knee-jerks were still present. During June improvement continued and he could walk uphill and swim several hundred yards in the sea. On June 25 he resumed duty.

From about the middle of June he had noticed that the thumb over and round the healed wound was very numb to touch and even to pressure. This impairment of sensation he observed to increase slowly in degree and extent, spreading over the whole hand and up the forearm. During July the right hand became clumsy, writing became difficult, and at each attempt his handwriting rapidly became untidy and laborious to continue. In addition, the hand was awkward in all movements and the grasp weak.

Simultaneously he began to find going upstairs difficult, his knees felt as if they were going to collapse under him, and the legs ached on exertion.

Tingling and 'pins and needles' sensations then appeared in both feet and also in the left hand. Three days before readmission to hospital (15/7/17) he had to stop writing on account of cramp and loss of control over the fingers.

No defect of vision, deglutition, or speech.

On examination (18/7/17):

The cranial nerves were perfectly normal. The right arm was definitely very weak and all fine movements were wildly ataxic, especially with the eyes closed. This ataxy was clearly sensory in type and all the phenomena of loss of position sense were present: falling away of the extended hand, 'pseudo-athetosis', and error of projection in the finger-nose test when the eyes were closed.

The muscles were flabby and all distinctly weaker than those of the left

arm, which also showed slight general weakness and some ataxy. Both legs were flabby and very weak, the dorsiflexors being especially affected. To pressure the calves were very tender.

Walking was normal in appearance until after very slight exertion, when a tendency to foot-drop appeared. There was slight Rombergism.

The sensory system showed marked changes of the usual peripheral type—impairment of touch, pain, temperature, and deep sensibility in the distal segments of the limbs, most marked in the extremities. The whole of the right hand was completely insensitive to touch and pin-prick and the loss was more profound and extended farther up this arm than up the left. All tendon jerks were abolished. Abdominal and plantar reflexes were normal. Heart and urine were normal.

After three weeks' rest in bed the sensory and motor symptoms began to recede, but the right arm remained definitely the most affected limb. The tendon jerks had not returned when last examined in August.

There was never any trace of cranial nerve involvement.

This case is particularly valuable since the patient himself was a medical officer and a most careful and skilled observer. It constitutes a definite example of an extensive diphtheritic paralysis beginning locally in the inoculated limb and then becoming generalized in the spinal nerves. The cranial nerves were never affected in the slightest degree. The association of this condition with a diphtheritic infection is also certain, and there would seem little room for doubt that the case is a true lymphogenous ascending infection of the central nervous system along a nerve.

Case III. Diphtheritic infection of a gunshot wound of the lumbar region followed by peripheral neuritis, affecting mainly the lower limbs and showing no cranial nerve involvement.

Pte. H. B. was wounded in the 'small of the back' on the right side on April 19. There were two wounds—exit and entry—about 6″ apart, just above the left buttock on the dorsal aspect. On April 27 the bullet track was laid open for drainage.

During May the wound became very septic and sloughs formed on the surface, and in spite of daily eusol dressings and hip baths the wound remained unchanged and covered by greyish sloughs. Sun baths and other devices influenced it but little.

During the month of August, while a fairly large raw surface still remained, the patient began to get about more freely and at once complained of numbness and tingling in the feet and the palms of the hands and of weakness and aching in the muscles of the legs.

He came under my observation for these symptoms on August 23. Examination revealed a large almost healed scar, 6″ x 1½″, above the left buttock; the skin was adherent, purplish in colour, and shiny. At its centre was a small scab showing a pink granulating surface when removed.

The nervous system:—Cranial nerves were normal.

Slight general weakness of both upper limbs and slight sensory ataxy. The legs showed more marked flaccid weakness, with especial involvement of the dorsiflexors. The calves were moderately tender to pressure. There was well-marked sensory loss over all the extremities of the type seen in peripheral lesions. Position sense was profoundly impaired in the toes and this gave rise to some Rombergism. He could walk, but was readily fatigued. The tendon reflexes were abolished in all four limbs.

Examination of the wound gave a pure culture of typical Klebs-Loeffler bacillus. Capt. L. Hirst, R.A.M.C., made the following report on this:

'Report on a bacillus isolated from a swab from No. —, Pte. H. B.

The diphtheroid bacillus present in the primary serum tube was isolated without difficulty in pure culture by plating on agar. Microscopically the organism was typical of a medium-sized Klebs-Loeffler bacillus showing marked beading and characteristic grouping. Gram-positive polar bodies were brought out by Neisser's stain and toluidine blue.

The appearance of the colonies on the plate and of the growth on serum and agar resembled that of the diphtheria bacillus.

After incubation for ten days in carbohydrate broth tinted with litmus the reactions were as follows: Acid in glucose and maltose. No change in lactose, saccharose, mannite, and dulcite. 1 c.c. of a twenty-four hours' culture in trypsinized broth containing abundant growth was injected subcutaneously into a 400-grm. guinea-pig with negative result.

This bacillus is therefore to be regarded as an attenuated strain of the Klebs-Loeffler bacillus.'

This well-defined polyneuritis associated with a diphtheritic infection resembles Cases I and II in the complete absence of cranial nerve symptoms. There was no local paralysis noted at the onset, but the lumbo-sacral cord clearly bore the brunt of the toxaemia.

Multiple Neuritis associated with 'Septic Sores'.

Writing on the pathology of Barcoo rot, a form of chronic superficial ulceration of the dorsal surface of the hands and forearms occurring in troops serving in the desert and commonly spoken of as 'septic sores', C. J. Martin (10) mentions the possibility of diphtheritic infection in connexion with these. The undoubted occurrence of mild polyneuritis in certain men suffering from these 'septic sores' is very significant.

During nine months eight such cases have come under my observation. Their symptoms and physical signs are remarkably constant and a brief account of one case describes them all:

Case IV. C. Q.-M. Sgt. G., aged 33, had served in Egypt since the Gallipoli evacuation and had enjoyed perfect health.

In May 1917 he suddenly developed four septic sores on his hands and one just below the head of the fibula on the outer aspect of the left leg. These spread quickly and reached a diameter of 1½" before healing, which was also rapid, set in. During the latter half of August he began to notice—the sores being as yet unhealed—numbness in the hands and feet and constant tingling in the fingers and toes. About September 6 he noticed difficulty in getting about—weakness, aching of legs and unsteadiness, and slight swelling round the ankles.

The left leg was much weaker than the right. He came under my observation on September 15 and showed a well-marked multiple neuritis: weak ataxic limbs, with tenderness of calves and tendency to foot-drop. Absent tendon reflexes in all four limbs and the usual sensory loss, in which position sense was most deeply affected.

As the sores are always healed when the cases come under the observation of the neurologist a definite proof of their diphtheritic origin is not obtainable.

The possibility of beri-beri was considered, but this can be excluded with

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reasonable certainty. Only in one case (that quoted) was there any history of oedema, and the diet of the troops was beyond cavil in all instances. I have little doubt that these will ultimately prove to be cases of true diphtheritic paralysis.

Conclusions.

There is, therefore, a weight of evidence which may be considered sufficient to justify us in concluding that diphtheritic paralysis, at any rate in the initial and most characteristic of its stages, that of cranial nerve involvement, is an ascending infection of the central nervous system: the toxin elaborated in the membrane passing up to the medulla in the perineural lymph channels of the cranial nerves innervating the tonsils and fauces.

Unfortunately the nature of the morbid changes in diphtheritic toxaemia has not been sufficiently elucidated to enable us to identify them conclusively with the pathological changes occurring in known lymphogenous infection of the central nervous system.

It has already been pointed out that of the cranial nerves involved, one at least, the oculo-motor nerve, bears no relation to the infective focus. We cannot therefore in this instance be dealing with an ascending infection of the nerve. A clinical study of the condition makes it seem highly improbable that the mechanism of production of the various cranial nerve palsies is other than a single one.

Very probably it is not the passage of the toxin up in the lymph channels of the nerves that produces the lesion giving rise to the paralysis, but its action on the central nervous system, that is, on the nuclei of the nerves involved, that constitutes the primary and essential lesion. The rarity with which, in both human and experimental diphtheria and in the observations of Orr and Rows, the peripheral nerves along which the toxin passes show any lesion of the axis cylinder or myelin sheath, and the constancy of central cell changes (Orr and Rows, Babonneix, Bolton), make this extremely probable.

As Sicard (16) has pointed out with regard to so-called 'ascending neuritis', we are not dealing with a neuritis at all, but with the passage of toxins along the course of the nerve. This may produce some inflammatory reaction in the lymph channels through which they pass, but not an actual neuritis. The lesion which gives rise to the symptoms is central.

In this respect then the views of Babonneix and of Guillain and Laroche need modification.

We have, however, still to consider the generalized paralysis which commonly appears somewhat later than the development of these cranial nerve paralyses. Clinically, this resembles in every particular a multiple neuritis. It has these characteristics, namely, that its onset is delayed, it appears simultaneously in all the spinal peripheral nerves, and it is more chronic in its course than the earlier cranial nerve symptoms.

In the generalized paralysis following the intravenous injection of diphtheria

toxin in animals (Bolton and Bown) there can be no question of a lymphogenous infection. Any involvement of the nervous system in this instance must be part of the general systemic toxaemia—an intoxication by the blood stream.

In every case of diphtheria the toxin circulates in the blood and must reach the nervous system, central and peripheral, by this channel.

Is the generalized paralysis of diphtheria in man, then, a blood as opposed to a 'lymphogenous' infection? The characteristics enumerated above are very significant in this connexion.

These points of difference might conceivably be due to a slow spread of the toxin in the cerebro-spinal lymph system, but are far more probably dependent on its relative dilution as it reaches the nervous system in the blood stream.

There seems then to be a twofold mechanism in the production of diphtheritic paralysis in man. There is the initial sometimes severe and relatively short-lived 'local' paralysis, due to the action of the toxin, which has ascended the nerves innervating the local lesion, on the nerve nuclei in the brain stem. Secondly, there is the later, longer-lasting 'generalized' paralysis, which is part of the general systemic toxaemia.

Such a mechanism would account for all the phenomena present in the ordinary paralysis of faucial diphtheria, and in that following wound infections, such as the cases recorded here.

In many wound infections, such as that recorded in Case III, it will be manifestly very difficult to detect an initial local paralysis. Only when the infective focus is in an extremity, e.g. Case II, can we expect to see definite 'local sign' in the paralytic phenomena.

If this hypothesis of the nature and pathogenesis of diphtheritic paralysis be correct, it is not surprising that the views of different observers on the pathology of the nervous system in this toxaemia are so conflicting and inconclusive. This aspect of the subject demands reinvestigation on the lines indicated in the researches of Orr and Rows.

In our present state of knowledge there is not even agreement as to whether the central or the peripheral nervous system is primarily affected.

What is true of the lesions underlying the bulbar symptoms may not be so of those manifested in the generalized paralysis. In the light of our knowledge of lymphogenous infections and guided by some definite conceptions of the pathogenesis of the condition, it should be possible to arrive at the true pathology of diphtheritic paralysis and thus to confirm the views put forward here.

In this paper the question of post-diphtheritic hemiplegia has not been mentioned. This is definitely proved to be embolic in origin and secondary to endocarditis. It does not therefore come within the limits of the subject.

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THE IMPORTANCE OF THE MECHANICAL FACTOR IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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With Plates 12 and 13

Introduction.

If a large series of cases of pulmonary tuberculosis be studied clinically, radiographically, and from the point of view of their reaction to treatment, it is surprising how rare it is to find any two of them which show any uniform similarity. Yet, despite this fact, there seems to be a tendency at the present time to classify the types of disease under a very few brief headings, and to distribute the patients for the purposes of treatment into as small a series of groups as possible. This method has had a considerable degree of success since the aim and object in each of the groups is, in a great measure, to increase the physical fitness of the patient and his capacity, therefore, to react to the disease. The success in the treatment has not, however, been as great as it is possible to obtain because the individuality of the case has been obscured by the group system, and because also the mechanical changes in the lungs and in the thorax have not been given sufficient attention. It is in this respect particularly that the individuality of the patient exists. It is true that in a very small proportion of cases the mechanical factor is dealt with, and collapse of the lung is obtained by introducing nitrogen into the pleural cavity; but even the rationale of this treatment is not always recognized, as is shown by the prejudice which still exists against it, and by the opinion which is still too often expressed that the treatment should not be tried except as a 'last resort'.

There are four factors which are of the utmost importance when determining the course of treatment most suitable for a patient suffering from pulmonary tuberculosis. They are:

1. The capacity of the patient's tissues to react against the disease.

2. The extent to which this reaction can be increased by hygienic measures, exercises, and so forth.

3. The extent and character of the mechanical changes which have already taken place.

[Q. J. M., April, 1918.]

4. The presence of accessory foci of chronic septic absorption (especially those of the nose, mouth, and pharynx).

It is on these four factors that the prognosis also must be based.

I do not intend to deal here with the first two and the last of these, but wish to discuss the mechanical changes that may occur and the various ways in which it is possible to overcome to a greater or less extent the symptoms they give rise to and the disadvantageous influence which these changes may in their turn exert on the course of the primary disease. It must, however, be clearly borne in mind that though I deal with the one factor as separate from the other three, yet in the actual treatment of a case it is of little use to treat the mechanical changes unless every available means is taken at the same time to maintain and to increase the general tone of the body.

The mechanical disabilities are due primarily to the anatomical and physiological conditions of the lungs and thorax, and secondarily to the fibrotic changes in the lung parenchyma, to the occasional formation of cavities, and to the interpleural adhesions which develop as a result of active or quiet (so far as symptoms are concerned) pleurisies. These disabilities are found in all chronic diseases of the lung, but are most evident in tuberculosis and bronchiectasis.

The primary causes are too well known to need more than brief reference. The lungs are enclosed in air-tight cavities bounded by semi-rigid walls and are kept in a state of expansion by a constant negative pressure. Diminution in the size of the lung must be accompanied, therefore, by an increase in the negative pressure in the pleural cavities, or by the yielding of one or more of the sides of the cavities. When the diminution in the volume of the lung is slowly progressive, it is rare to find an increase in the negative pressure equal to 2 or 3 mm. of mercury. The walls bounding the lung yield with difficulty; the mediastinum is the least rigid and the ribs the most, whilst the displacement of the diaphragm is dependent to a great extent on the presence or absence of direct pull on that muscle through adhesions. In children the flexibility of all the walls is considerably greater than in adults and diminishes steadily with increase in years.

In chronic pulmonary diseases there is always the formation of abnormal fibrous tissue due to the reaction in the lung to the irritation set up by the disease. The fibrous tissue contracts and there is, therefore, a progressive diminution in the volume of the lung. This exerts a constant traction on the surrounding walls, which in turn resist the process. There are thus two opposing forces at work, each interfering with the function of the other. On the one hand, there is the resistance offered to the contraction of the lung by the surrounding walls and by the intrapleural negative pressure; on the other hand, there is the constant pull of the fibrous tissue, exerted either through the negative pressure or by direct pull by adhesions on the thorax, on the mediastinum, and on the diaphragm limiting the normal movements of these parts and causing deformity.

The intrapulmonary fibrosis has also a striking influence on the bronchi,

giving rise to the most characteristic secondary changes associated with pulmonary tuberculosis and to a group of symptoms which are more difficult to treat even than those of the initial lesion. The morbid anatomy change is directly or indirectly a bronchial dilatation. The strands of fibrous tissue which radiate from the bronchi to the periphery are, as I have said, constantly contracting. If there was no resistance at the outer surface of the lung, the greater part of the force of this contraction would be exerted in collapsing the lung. Owing, however, to the resistance offered by the surrounding walls, the force of the contracting fibrous tissue is exerted on the walls of the bronchi as well as on the walls of the pleural cavity, and a direct bronchial dilatation ensues. When, however, the fibrosis is massive in character, there is strangulation of the larger bronchi: this leads to obstruction of the air entry into those areas of the lung supplied by the affected tubes, and later to a secondary bronchiectasis. The dilated bronchi are also sooner or later infected by saprophytic and pyogenic organisms.

The formation of fibrous tissue continues so long as there is any active tuberculous disease or secondary infection, either of intrapulmonary cavities or of dilated bronchial tubes. As regards the latter, the fibrosis which is responsible for the secondary infection is also aggravated by it and a vicious circle is established.

The fibrosis is the attempt on the part of the tissues to check the spread of the disease and to repair the damage which has been done by it. It may be successful so long as the process has not spread beyond the capacity of the surrounding structures to compensate for the contraction. If the disease and the associated fibrosis are of greater extent, then the usefulness of this new tissue formation is limited, is frustrated, or is even turned to disadvantage by the normal anatomical and physiological conditions.

A cavity in the lung differs very little from a chronic abscess in any other part of the body. If a bronchus affords free drainage of the cavity it remains comparatively dry and innocuous. But if, on the other hand, the drainage is inadequate on account either of the size or the position of the opening, then there is retention of secretions, secondary infection, toxic absorption, and the contained pus is usually offensive.

No deep-seated chronic abscess can heal while its walls are separated. Healing is difficult, even under the most advantageous circumstances, when the cavity is infected by tubercular as well as by pyogenic organisms. The approximation of the walls of a moderate-sized or large cavity in the lung must necessarily be a practical impossibility without adventitious assistance, unless the thoracic walls are extremely plastic. The most that can be done without surgical intervention is temporarily to reduce the infection in the cavity and possibly to effect some slight reduction in size by encouraging the free expansion of the more normal parts of the lung. So long as the cavity persists, however, it is always liable at any time to become re-infected.

The formation of interpleural adhesions is not necessarily preceded by a painful pleurisy. Nor does a painful pleurisy always imply the subsequent

adherence of the pleural membranes. The existence of adhesions enables the lung to exert direct traction on the surrounding walls. The effect of this on the diaphragm is to produce fixation and at times striking distortion of that muscle. One may infer from this that the distortion of the chest-wall is greater when adhesions are present than when the contraction of the lung exerts its influence indirectly (i.e. through the intrapleural negative pressure). Dense adhesions on the mediastinal aspect fix the mediastinum and so limit the displacement of the contained structures.

It is difficult to determine the precise extent to which these abnormal mechanical conditions may be responsible for symptoms, may interfere with treatment, and may affect the prognosis of the case. Their adverse influence is in certain respects unquestionable, but in others it is more problematical. These mechanical conditions are without doubt responsible for the secondary changes which occur in the bronchial tubes, changes which are accompanied by symptoms of chronic bronchitis or of secondary infection. They are the main factor in the causation of shortness of breath, in that the free expansion of the lung is inhibited either by the direct contraction and resistance of the strands of fibrous tissue, or by the obstruction of free air entry into the alveoli by massive fibrosis round the bronchial tubes; thus interfering with the correlated rhythm of the lung and of the thorax during respiratory movements. They are responsible, in certain cases, for the retention of secretions, and they interfere with the free blood supply and lymph flow in the affected area or areas of the lung. They may be the determining factor in the formation of cavities; they certainly prevent their collapse, thereby interfering with the healing processes and encouraging the occurrence of secondary infections and of ulceration of the exposed vessels. Lastly, when the visceral and diaphragmatic pleural membranes are adherent, the contraction of the fibrous tissue leads to distortion of the diaphragm, which change is at times accompanied by a constant and extremely distressing dry cough.

The contraction of the chest-wall, the displacement of the mediastinum and its contents, and the compensatory emphysema of the unaffected lung areas are also the product of the diminution in the volume of the lung due to the fibrosis. These changes are the effort on the part of nature to counteract the abnormal mechanical factors. In the earliest stage of the disease they may be actually sufficient to produce adequate compensation for the mechanical disabilities. An early case of pulmonary tuberculosis may in fact be defined as one in which the changes in the surrounding structures (i.e. the contraction of the walls and the emphysema) have been able to keep pace with the fibrous contraction of the diseased part of the lung: in other words, they have been able up till then to compensate for the mechanical disabilities. As the disease progresses, the extent of this natural compensation is increasingly limited, and later is totally inadequate. The secondary changes in the lung now manifest themselves, and they may eventually become the predominating feature. Once the pathological changes have exceeded the limits of easy compensation it must necessarily follow that

the success which can be obtained by methods of treatment, which do not include the means of artificially compensating for or of overcoming the mechanical disabilities, must be limited or must fail.

The rationale of all modern surgical intervention for the treatment of pulmonary tuberculosis is the readjustment of the normal, physiological, and anatomical conditions of the lung and of the walls surrounding that organ, so as to accommodate them to and compensate for the mechanical disabilities due to the various pathological changes which have taken place in the lung and in the pleural cavity. The operations are designed to remove those disabilities which are an almost insuperable bar to the successful treatment of the patient by hygienic or other medical forms of treatment. But each of these surgical measures possesses other advantages: they have a direct beneficial effect on the disease, on the symptoms of the disease, on the secondary complications, and, therefore, on the general health of the patient and his power of resistance to the invasion of the tubercle bacilli. They do not all of them shorten the time during which the patient has to receive treatment, but they very materially lessen the period during which he has to abandon all work and to devote himself exclusively to the task of attempting to combat the primary disease and its complications.

The Methods of Operative Intervention.

Four methods are available,[1] namely: 1. Displacement of the lung by nitrogen (artificial pneumothorax). 2. Local displacement of the lung and of the parietal pleura by foreign substances. 3. Displacement of the whole lung and of the chest-wall by rib mobilization. 4. Paralysis of the diaphragm by section of the phrenic nerve.

1. *Nitrogen displacement.* In a normal person it is possible to obtain complete collapse of the whole of one lung by injecting nitrogen into the pleural cavity. The lung is collapsed round its root; there is no longer a negative intrapleural pressure, and the respiratory movements of the chest-wall and of the diaphragm exert comparatively little influence on the lung. In a patient suffering from pulmonary tuberculosis, the completeness of the collapse of the lung may be interfered with by intrapleural adhesions or by intrapulmonary changes such as massive fibrosis and pneumonic consolidation. The limitation in the extent of the collapse due to the intrapulmonary changes is only very rarely sufficient to affect adversely the advantages which may be expected from this method of treatment. Interpleural adhesions, on the other hand, may be so widespread as altogether to prevent the introduction of gas, or by their extent or character they may seriously limit the displacement of the organ. In the absence of these complications the collapse of the lung, which can be obtained by displacement by nitrogen, offers a comparatively simple and extremely satisfactory

[1] The treatment of ingravescent pneumothorax due to spontaneous rupture of the lung is not included here, but will be discussed later.

means of compensating for the mechanical disabilities brought about by the disease.

The presence of gas at atmospheric or at a positive pressure in the pleural cavity removes that constant tension on the surfaces of the lung which interferes with the contraction of the fibrous tissue. This is now able freely to contract without dragging on the walls of the bronchi. Cavities due either to dilated bronchi or to disintegration of the lung parenchyma become obliterated and their walls approximated; there is no longer, therefore, retention of secretions, and consequently the absorption of the toxins due to the secondary infections is greatly diminished and the danger of a haemorrhage by ulceration into an artery is abolished. The symptoms also associated with these pathological changes—pyrexia, cough, sputum—diminish in a striking fashion or disappear. The lung which responded inadequately to the enlargement of the chest during inspiration, owing to the resistance of the fibrous tissue, is now placed at rest, and the shortness of breath is consequently diminished. The patient's general condition improves immediately with the diminution of the symptoms, with the absence of septic intoxication, with the improvement in the night sleep and of the appetite. The ability to do an increasing amount of work without aggravation of the symptoms leads to a steady improvement of the power of resistance to the primary infection.

I have already, in other papers, described the technique of nitrogen displacement,[2] and there is, therefore, no necessity to describe this again. Recent experience has, however, led me to modify my opinion on three points. During this last summer I have started twelve new cases, and only one of these patients have I kept rigidly confined to bed during the preliminary injections. After the first two injections the patient has remained in bed for forty-eight hours so that his reaction to the treatment could be exactly estimated. After the subsequent injections the patient has been allowed to get up in from twelve to twenty-four hours unless there were any special symptoms which contra-indicated this course. Whereas previously some 3,500 to 4,000 c.c. of nitrogen were required to bring about complete displacement of the lung, in all but one of the last series practically twice as much gas was required. The exception was the patient who was kept in bed during the whole period of time of induction of the artificial pneumothorax on account of tachycardia, the result of prolonged septic intoxication. This increase in the amount of gas required is due to the exercise promoting more rapid absorption.

The period of six weeks which I have formerly advocated as being the maximum time which should elapse between the first few refills is, I am now certain, too long an interval. For the first six months the refills should be done at intervals of not more than a month.

It is usually stated that about 33 per cent. of patients treated by nitrogen displacement develop some fluid in the pleural cavity. In none of the cases above mentioned did an effusion occur, and in one patient only of the previous

[2] *British Medical Journal*, March, 1914; Choyce's *System of Surgery*.

series.[3] An effusion may be the result of trauma to the pleura, or of rupture of adhesions, but I believe that in the large majority of cases it is an indication of a mild infection.

All patients who are being treated by nitrogen displacement should be examined periodically with the X-rays. This is the only certain means of ascertaining the manner and extent of the displacement and the position and character of any adhesions which may be present. It is by means of the X-rays only that it is possible to determine when the collapse of the lung is complete. Neither the amount of gas run in, nor the pressure of that gas, nor the displacement of the heart affords reliable evidence. The displacement of the heart depends largely on the mobility of the mediastinum. A positive pressure may indicate complete collapse of the lung, but it may equally well be present when the displacement is only partial, and is then due to adhesions or to the resistance offered by the intrapulmonary fibrosis or consolidation.

In comparatively few cases of pulmonary tuberculosis are the pleural membranes completely free of adhesions: these were present in every one of the twelve cases of my last series. The character of the adhesions varies greatly: they may be almost universal, and the treatment is then impossible; they may be few in number but dense in character, or multiple but slender. The treatment in every case in which adhesions are present must vary with the character of them, and this can only be determined with the X-rays. When the upper lobe is adherent to the dome of the pleural cavity and the remainder is free, the whole organ is displaced in an upward and inward direction, and the collapse is often as efficient, though not as complete, as in a case free of all intrapleural fibrosis.[4]

Fixation of the lung to the diaphragm by a basal pleurisy is often an annoying complication, as with collapse of the lung there is constant traction on and displacement of the muscle. This at times is comparatively symptomless, but usually there is a dry irritating cough which may be paroxysmal in character when the patient exerts himself, or it may be the constant accompaniment of all actions such as laughing, sighing, or the taking of a deep breath. This symptom lessens as the gas in the pleural cavity is absorbed and the lung re-expands, but with each refill it occurs with the same irritating persistence. In all cases in which the basal adhesions are directly interfering with the treatment, it is advisable to paralyse that side of the diaphragm by section of the phrenic nerve in the neck. The results obtained by this treatment will be considered later.

In one case in which the characteristic symptoms due to traction on the diaphragm developed as a result of nitrogen displacement, I paralysed the

[3] All these patients were examined constantly by the X-rays.

[4] In one of my cases in which this condition was present, the displacement of the lung into the upper part of the pleural cavity was immediately effectual in reducing to normal the temperature, which had shown a nocturnal rise of 2 or 3 degrees for several months. There was a corresponding abatement in all the other symptoms.

phrenic nerve by the injection of absolute alcohol. Although I was successful, it is not a method that I would advocate unless the patient refuses operative treatment. The chances of satisfactorily infiltrating the nerve, using a small quantity of alcohol only, are uncertain, owing to the difficulty of gauging the exact thickness of the overlying structures.

The systematic radiographic examination of all cases of tuberculosis undergoing nitrogen displacement will show the greatest variation in the number, the thickness, and the position of adhesions.

A broad dense adhesion will yield very little to the constant displacement of the lung by nitrogen. The medium-sized adhesions will stretch; some of them sufficiently to enable full displacement of the lung to be obtained. The finest of all will rupture, at times with even a quite small intrapleural positive pressure. The actual separation of adhesions occurs probably during an act of coughing and may be accompanied by a slight momentary pain.

Adhesions which interfere with efficient collapse of the lung, but which allow sufficient displacement to enable the character and extent of the bands to be recognized by radiography, can be dealt with in three ways: (*a*) By rupture; (*b*) by stretching; (*c*) by division.

(*a*) *Rupture.* This treatment is justifiable only when there are multiple strands traversing the pleural cavity, and when rupture can be effected by raising the intrapleural tension by a pressure of gas equal to not more than 20 mm. of mercury. I have on one occasion raised the intrapleural pressure for this purpose until it equalled 32 mm. of mercury; but in this case there was a profusion of strands traversing the space between the lung and the chest-wall, and the condition of the patient was hopeless unless a considerable displacement of the lung could be effected. The radiogram showed, moreover, that the visceral pleura was less likely to yield than a number of the adhesions: in order to minimize the risk of a pleural reflex, one-third of a grain of morphia had been given previously. The patient describes the sensation, at the moment of rupture, as of something giving way inside the chest; the manometer shows an abrupt fall in the pressure and an increase in the respiratory variations.

(*b*) *Stretching.* Medium-sized interpleural bands may be stretched by maintaining a fairly steady positive pressure (equal to about 8 or 10 mm. of mercury) for a considerable period of time (two or three months). Refills are necessary during this period every eight to ten days. By this means I have succeeded in getting almost complete displacement, nearly doubling the amount of the collapse which was at first permitted by the resistance of the adhesions.

The constant stretching of adhesions by pressure is, as a rule, symptomless. Occasionally however, and more particularly if the peripheral end of the adhesion is attached to the diaphragm, slight pain is experienced. Rupture of adhesions may cause a slight pleural effusion; stretching practically never does.

Neither of these two methods of treatment is justifiable unless the processes can be continually controlled by radiography. It may almost be said that it is dangerous to inject gas into the pleural cavity once the intrapleural

tension is positive, unless an accurate knowledge of the intrapleural conditions has been obtained by the X-rays. One case will help to emphasize this point. A positive pleural pressure had been reached, but it was obvious from the amount of gas which had been run in that the displacement of the lung was incomplete. Radiographic examination revealed that there was a single stout adhesion running from the surface of the lung to the pleura; the central end was situated over a superficial cavity the outer wall of which had become cone-shaped from the drag of the fibrous strand. A further increase of intrapleural pressure would have, in all probability, resulted in the rupture of the outer wall of the cavity. Such an adhesion cannot be treated by stretching, but by division only.

(*c*) *Division.* The presence of a single or even of two or three interpleural bands, which allow a partial collapse of the lung only but which will not yield further to the constant influence of an intrapleural positive tension, must not be permitted to interfere with the success of the treatment by nitrogen displacement. Such adhesions are usually attached to the lung opposite the area most affected by the disease, and consequently that part of the organ which should be the most collapsed is the least displaced. There is one situation in which a single band-like adhesion is found with great frequency. The central end is attached to the lung near the lower border of the upper lobe, whilst the peripheral end is fixed to the parietal membrane opposite the second rib in the front of the chest, at the side, or posteriorly. The band may be narrow and cylindrical or broad and flat; the latter is more resistant to stretching than the former. If a radiogram shows that such free bands of adhesions are the sole cause of preventing further collapse, and if at the end of a month it is clear that they will not yield to the stretching force applied, they should be divided. Before such an operation is undertaken the direction of the adhesion and the points of attachment must be determined as accurately as possible. The method of approach and of division varies with the type of the band. Those which are over one inch in length are most satisfactorily divided by a special tenotome passed through the chest-wall, the field of operation being rendered visible by X-ray illumination. When the adhesion is short and broad it is not suitable for this method of division, and access must be obtained by opening the chest at a point as close to the band as possible. This section by direct division is rarely indicated, but division by what may be termed indirect vision (X-ray illumination) is much more frequently necessary. The following are the steps of operation:

The day or two before, an injection of gas should be given so as to tighten the band by displacing the lung as far as it will go. Two hypodermic injections, each of a quarter of a grain of morphia, are given, the one half an hour and the other immediately before the operation. The patient lies on a couch with the X-ray tube beneath, while an assistant holds the screen. The tube should be fitted with a diaphragm so as to limit the rays to the field of operation. It is advisable for the surgeon to wear smoked glasses, which are removed only

when the X-rays are turned on. When the peripheral attachment of the adhesion is to the front of the chest, the tenotome is passed into the pleural cavity through an intercostal space in the mid-axillary line, but if the adhesion is fixed to the lateral or posterior aspect, the tenotome is passed through the front of the chest.

The tenotome which I had made for this purpose has the blade 2 cm. long by 0·6 cm. broad, sharpened at both edges, and gradually increasing in thickness to the shank. This part of the instrument is 12·5 cm. long, and has the same breadth and thickness as the base of the knife, but the edges are rounded. It is in turn attached to a short handle. The shank passes readily through the incision in the chest-wall made by the blade of the tenotome, but fits so closely into it that there is no escape of air. The wound through the pleura closes on withdrawing the knife, and unless there is an immediate fit of coughing, there is no subsequent escape of gas into the cellular tissues. The track through which the tenotome passes is previously anaesthetized with novocaine.

As soon as the tenotome is in the pleural cavity, the room is darkened and the X-rays are turned on. Both the adhesion and the tenotome are now visible, and the latter is directed towards the former till the edge of the knife rests on the band. The resistance which this offers to the knife can be felt and the movement of the band and of the lung produced by the pressure of the knife can be seen. The adhesion is cut through by sawing movements.

A little blood may escape from the cut edges if the adhesion is a broad one, but the bleeding soon stops and is of no material consequence. The patient is kept quite quiet for the next twenty-four hours, but beyond this no special after-treatment is necessary.

2. *Local displacement of the lung and of the parietal pleura by foreign substances.* This form of treatment is strongly advocated by Tuffier. It is applicable only to those cases in which the disease is limited to one lobe and in which nitrogen displacement is impracticable. Advantage is taken of the fact that even when the two pleural membranes are firmly united by the products of inflammatory action, it is still possible to strip the parietal membrane from off the deep surface of the chest-wall. Such displacement cannot be maintained by injections of gas, as there is no limiting membrane on the outer surface to prevent the escape of gas into the cellular tissues. It is for this reason that the extra-pleural space is filled up by some solid substance. The foreign substances used are of two characters: (1) Paraffin, or pastes of which paraffin is the basis; (2) transplanted living tissues, e. g. lipomata, omentum, fibromata. The best results have been obtained with the living tissues.

The indications for this treatment are that the disease is localized, is complicated by considerable mechanical changes, and that the pleural membranes are adherent. It is obvious that such cases are comparatively infrequent.

3. *Displacement of the whole lung and of the chest-wall by rib mobilization.* In every case in which collapse of the lung by nitrogen displacement has been

tried but has failed owing to the density of the adhesions, the advisability of obtaining collapse of the lung together with the chest-wall by rib mobilization must be considered. Rib mobilization places the whole lung permanently out of action, and there is no possibility of allowing re-expansion of that organ should there be spread of the disease to the opposite side. In the cases selected for nitrogen displacement, the presence of some disease in the second lung is not necessarily any bar to this method of treatment. But when determining on the suitability of a case for rib mobilization, the presence of any active tubercular disease whatsoever in the opposite lung should always negative the operation. A small quantity of fibrosis is not necessarily a contra-indication. Myocarditis and a rapid pulse due to prolonged septic intoxication are usually improved when collapse can be obtained by nitrogen, but these conditions must be regarded very seriously when considering the question of rib mobilization. It is only a few of those cases, therefore, in which treatment by nitrogen has been tried and failed that are suitable for rib mobilization. The number is still further reduced by the exclusion of those in which the disease is localized to a part only of one lung and in which treatment by nitrogen has been advised because the lesion is progressive or remains chronic despite hygienic measures, or because it has been desirable to enable the patient to resume his occupation at the earliest moment possible. For such localized disease rib mobilization may occasionally be necessary, but a much longer period of time should be allowed for the trial of other and less drastic measures.

In suitable cases—that is, in those in which there is a chronic unilateral tubercular fibrosis and especially in those in which the primary disease is complicated by secondary infection, by cavity formation, and by bronchial dilatation (Plate 12)—rib mobilization will yield most gratifying results. In many respects it is a much more efficient method of treatment than nitrogen displacement because the collapse of the lung once obtained is constant and is permanent. The operation is one, however, which must not be undertaken lightly, or until the fullest examination has been made and consideration given to all the aspects of the case. But the mortality is low and the end results are now sufficiently established to necessitate a more universal recognition of this method of treatment for pulmonary tuberculosis.

I have given a full description of the technique in the *British Journal of Surgery*, vol. ii, No. 8, 1915.[5]

4. *Paralysis of the diaphragm by section of the phrenic nerve.* The object of this operation is, equally with the preceding, to compensate for the mechanical disabilities due to the intrathoracic changes produced by pulmonary tuberculosis. The treatment differs, however, from those above described, in that it has very little direct effect on the course of the primary disease; its value is as an adjunct to other forms of treatment by relieving certain distressing symptoms, and by preventing the establishment or the spread of some of the most serious complications.

[5] 'The Operation of Rib Mobilization for the Treatment of Phthisis.'

I have already called attention to the advantages gained by paralysing the diaphragm when the pull of the lung on that muscle through adhesions, as the result of the collapse of the lung by nitrogen, produces a constant cough. In some cases of extensive fibrosis there is striking distortion of the diaphragm independent of any displacement of the lung by surgical intervention. A 'diaphragmatic' cough is an occasional accompaniment of this change, and complete relief can be afforded by section of the phrenic nerve.

The phrenic is readily accessible for division in the neck immediately above the clavicle, where it lies on the scalenus anticus muscle under cover of the sterno-mastoid. The operation is done under local analgesia. The resulting paralysis of the corresponding half of the diaphragm is, as a rule, complete. That part of the muscle relaxes, and with the X-rays the arch is seen to occupy a position about one inch higher than normal and during quiet respiration to be stationary. During deep inspiration the paralysed half of the muscle rises still higher into the thorax. Very occasionally a considerable portion of the nerve fibres for the diaphragm are conveyed to the phrenic by way of the nerve to the subclavius muscle. Section of the phrenic in the neck is then followed by a paresis only of the corresponding half of the diaphragm (Plate 13).

Since paralysis of the diaphragm is accompanied by an upward displacement of that muscle, it is obvious that there must be a corresponding diminution in size of the base of the pleural cavity and of the lung; and in addition considerable diminution of expansion of the lower lobe during inspiration, as this depends mainly on the downward pull of the diaphragm. The collapse of the base of the lung is not sufficient to make the benefits immediately apparent, but the diminution in the volume of the lobe and the removal of the constant drag on the fibrous tissue must very materially compensate for the existing, and check the further development of the mechanical disabilities. Paralysis of the diaphragm may therefore be regarded as a prophylactic measure against the production or the increase of bronchial dilatation in the lower lobe.[6]

There are thus four separate methods of combating and of compensating for a whole or a part of the mechanical disabilities which develop during the progress of or during the processes of reaction to the disease in cases of pulmonary tuberculosis. Of these, the displacement of the lung by nitrogen is the method of choice in all cases in which it can be carried out. It is without danger, if suitable precautions are taken; the technique is extremely simple in straightforward cases, but considerable experience is required to obtain the best results, since the conditions vary so in every case that it may truly be said that each patient requires individual treatment. The patient is not necessarily confined to bed during the treatment, and the period of his convalescence is greatly reduced. The displacement can be maintained for as long or as short a time as

[6] It is for this reason that I advocate section of the phrenic nerve in cases of chronic interstitial basal pneumonia, since these cases, if left untreated, almost invariably develop progressive bronchial dilatation. Influenzal pneumonia is the commonest precursor of bronchiectasis.

required. When the collapse of the lung is complete, the symptoms disappear rapidly and usually completely, if the disease is unilateral; they are greatly reduced in bilateral cases. The lung is at rest and the primary disease is placed in those circumstances most antagonistic to the spread of the tubercle bacilli.[7] The secondary infections are reduced by the obliteration of those spaces which favoured the development of them; the danger of secondary haemorrhage is abolished; the fibrosis is no longer interfered with by extra-pulmonary conditions, and is in turn not able to exert its harmful influence on the intrapulmonary tissues. As the result of these changes, the general health of the patient improves with increase in appetite and better sleep. The increase in tone implies an increase in capacity to react against the disease, not only in the side under treatment but in the opposite lung also. Finally, it is possible for these patients to return to their work without danger to themselves or to the community after a period of time which is very greatly less than if the displacement had not been established.

The presence of adhesions necessarily limits the rapidity and possibly also the extent of the improvements. For this reason the stretching or the division of adhesions is always indicated when practicable.

Collapse of the lung by rib mobilization has the same effect upon the disease and its complications as has collapse by nitrogen displacement, but the operation is more drastic and the displacement is permanent. The number of suitable cases is, therefore, very limited, since the presence of active disease in the opposite lung is a necessary bar to this treatment.

Cases suitable for local replacement of part of the lung and of the parietal pleura are also few in number. There must necessarily also be a considerable difficulty in obtaining a mass of living tissue sufficient in size to effect the required degree of displacement.

Lastly, paralysis of the diaphragm has a direct beneficial effect on basal tuberculosis. The indirect value of it is considerable both as a check to the diaphragmatic type of cough and as a prophylactic measure against the increase of secondary bronchiectasis and the infection of the lower lobes.

Reference has been made previously to the cases of pulmonary tuberculosis in which the fibrosis is massive in character, resulting in obstruction in the air entry into the alveoli and later extensive bronchial dilatation. This type in its earlier stages will improve under treatment by nitrogen displacement; but in the later ones, when the bronchial changes are advanced, more satisfactory results are obtained by rib mobilization.

The fibrous tissue changes in the lung which persist after arrest of the disease are of a different character to those present whilst the pathological processes are in an active state. With cessation of the irritation due to the presence of disease, there is progressive modification and refinement of the masses of fibrous tissue. There is always a scar to show where the disease has

[7] This part of the subject I have dealt with in another paper, 'The Necessity for the Fuller Consideration of the Local Processes of Disease and Repair', to be published shortly.

been, but the coarse fibrous bundles become gradually absorbed and replaced by fine radiating strands which have comparatively little power to produce further morbid changes.

During the spring and early summer of this year (1917) I have had the opportunity of examining and of treating with Dr. Kincaid some eighty patients suffering from pulmonary tuberculosis. As a result of the presence of mechanical disabilities, nitrogen displacement was attempted in twelve cases; in three of these it was abandoned owing to the extensiveness of the intrapleural fibrosis. Most of the remaining nine had some form or another of adhesions. In one, fine strands were ruptured. In three, adhesions were stretched by maintaining a constant intrapleural positive tension. In one, an adhesion was divided; in one, the diaphragm was paralysed by the injection of alcohol into the phrenic nerve to abolish the symptoms due to the pull on the muscle by diaphragmatic adhesions. In all nine cases there was marked diminution of the symptoms and a corresponding improvement in the general condition.

In two patients, in whom there was considerable secondary bronchiectatic change in one lower lobe, the diaphragm was paralysed by section of the phrenic nerve. In one patient, who developed a pleural effusion, the fluid was replaced by oxygen and the displacement of the lung was subsequently maintained by nitrogen. Treatment also was necessary in one case in which a spontaneous ingravescent pneumothorax developed.

Brief allusion must be made to the treatment of this condition. If the symptoms are urgent and threatening the life of the patient, instant relief can be obtained by passing a large-sized hypodermic needle through the chest-wall. This needle is fixed in position by thread and strapping, and the outer end should be covered with a few layers of sterilized gauze.

When the symptoms are less acute it is possible, while allowing for the escape of the excess of air in the pleural cavity, to maintain a constant slight positive intrapleural pressure. This is particularly desirable as, unless the opening in the lung closes soon after the rupture and is prevented from being repeatedly reopened by the exertion of coughing, there is the danger of a permanent fistula resulting. The method of regulating the pressure is as follows:

If the needle which passes through the chest-wall is connected by tubing to a Wolff's bottle partly filled with water, the depth of the opening of the tubing below the surface of the fluid can be altered so that the gas will escape whenever the intrapleural pressure exceeds the required maximum; this should be equal to about 5 mm. of mercury. It will be found, however, that a cough raises the pressure considerably above this. With each cough there will be an escape of gas, and if the opening in the lung has closed, the intrapleural pressure will become progressively less positive and then more negative. To obviate this, the Wolff's bottle must be replaced by a horizontal spiral of some four turns of narrow glass tubing, the distal end of which opens into the base of a broad cylindrical receiver. The spiral coils should be $1\frac{1}{2}$ in. in diameter. The receiver must be broad, so that when the fluid is displaced into it from the

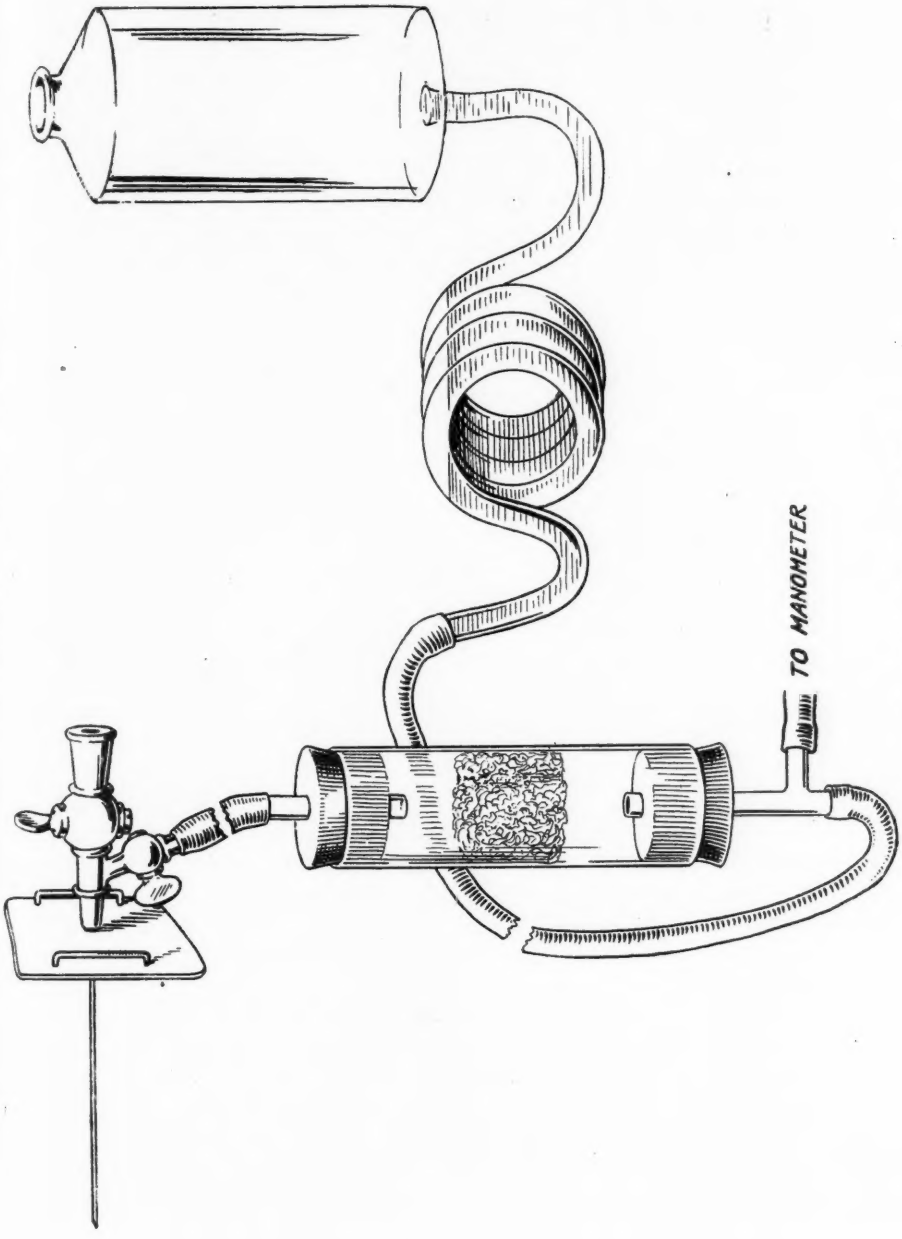


FIG. 1. For description see text pp. 218, 220.

spiral tubing the depth of water is not increased more than half an inch. Above, it is in direct communication with the open air; the spiral and receiver must be below the level of the patient. The intrapleural pressure is regulated by the extent to which these are filled with water. The water in the succession of loops of tubing prevents the escape of gas when the pressure in the pleural cavity is momentarily, even though considerably, raised by acts such as sneezing and coughing. When, however, there is a steady rise of pressure, the water is displaced from the spiral into the receiver and gas escapes until the intrapleural pressure is again equal to the height of the column of water (Fig. 1).

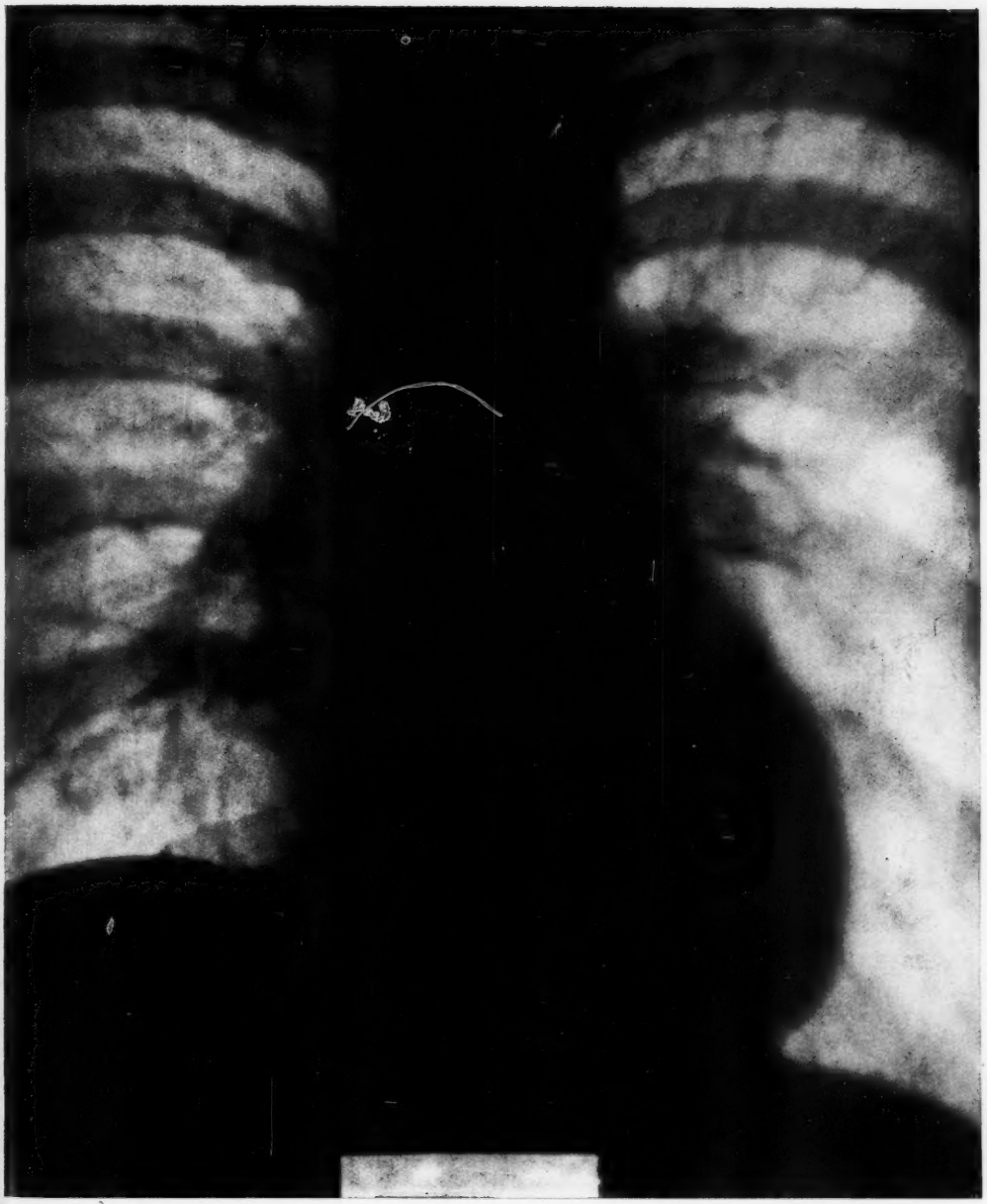
In conclusion, a word must be said on the advisability of carrying out the operative treatment for pulmonary tuberculosis in sanatoria as opposed to hospitals or nursing homes. A considerable experience of both enables me to assert without hesitation the desirability of the former, provided always that the necessary facilities are available. The results obtained in hospitals and nursing homes may be extremely gratifying, but one is often hampered by the inability to give to the patient those advantages which are to be obtained in a fully equipped sanatorium only. Nitrogen displacement need scarcely interfere with the special routine of sanatorium life, and if the X-rays are available, as they always should be, the treatment can be carried out under complete control.

The time required for the operations and for the immediate convalescence when rib mobilization is done is about eight weeks. It is an inestimable advantage to the patient if that time can be spent away from the stagnant and depressing atmosphere of a town, in a sanatorium where the air is fresher, the outlook more extensive, and the patient, when sufficiently recovered, can be wheeled from his room into the grounds. For it to be possible for these operations to be done in a sanatorium, however, the place must be properly equipped and nurses competent for the care of surgical cases must be available.

At present the importance, and even I may say the necessity, for the closest alliance between surgery and medicine in the treatment of pulmonary tuberculosis has not been appreciated. When this comes to pass, the equipment of a modern sanatorium will include facilities for radiography and for operative treatment.



Bronchial dilatation of the right lower lobe (compare with Plate 13).



Same case as shown in Plate 12. Paralysis of the right dome of the diaphragm by division of the phrenic nerve.

THE BONE CHANGES OCCURRING IN VON RECKLINGHAUSEN'S DISEASE

By ERIC PEARCE GOULD

(Based upon an investigation carried out in the Laboratory of Prof. Ludwig Pick, Friedrichshain, Berlin)

With Plates 14 and 15

SINCE von Recklinghausen published, in 1882, his monograph *Fibrome der Haut*, our conception of the disease which since then has borne his name has undergone a definite change. His work dealt solely with the relation of the peripheral nerves to the cutaneous nodules of molluscum fibrosum and the subcutaneous tumours associated with them, the whole condition being looked upon as a disorder of these nerves and their terminal cutaneous twigs.

The disease is by no means a rare one, and occurs throughout the world, Adrian having collected by 1903 as many as 407 cases. Closer investigation has brought to light additional features in the disease; thus it is now proved to be sometimes hereditary in origin, frequently congenital, and the following symptoms, in addition to the neurofibromatosis, are constantly found:

1. Pigmentation of skin.
2. Mental deficiency.
3. Changes in the skeleton.
4. Changes in the joints.

Few cases indeed present the complete picture of all these, and in different instances all possible combinations of three or more symptoms are to be met with, but it is quite clear that the disease can no longer be looked upon as a disease of the peripheral nerves, but of the whole nervous system, in which one or more of the ductless glands may be concerned.

The changes in the skeleton with which this paper deals resembled in post-mortem macerated specimens those of osteomalacia (Fig. 1), and are stated to occur in a degree noticeable during life in about 7 per cent. of all cases. But there appears to be no account on record of the microscopic appearances of such bones, without which it is impossible to decide whether the change is identical with that of osteomalacia proper. I have had the opportunity of examining

[Q. J. M., April, 1918.]

histologically portions of the skeleton of five cases. One of these showed the typical changes of 'osteomalacia' during life and post mortem; in one other the bones at the autopsy were decidedly soft, although there was no gross skeletal deformity. The remainder were apparently free from any softening at all. The microscopical findings agreed with this—that is to say, in one there was found marked pathological changes, in one other similar changes much less marked; the remainder presented in every section the picture of normal bone.

The clinical record and post-mortem notes of Case I are as follows. (The notes of the other four are given separately at the end.)

O. G., workman, aged 55, died November 17, 1910.

History. Healthy till 25 years of age, with the exception of children's ailments. From that time he noticed the appearance on chest and back of numerous small nodules. At the age of 41 he found he was becoming unable to work. At the same time he was troubled with occasional incontinence of urine. No history of similar disease in the family. Syphilis and alcohol excess negative.

State on admission to hospital. Medium-sized man of feeble muscular development. Over the whole body were scattered fine tumours varying in size from a pea to a bean: they presented no regular arrangement, and neither tumours nor the areas of skin between were tender on pressure. Skin reflexes normal. Knee-jerk on the right side plus, also Babinski right foot. Walking and standing without help impossible. Patient very deficient mentally. Heart and lungs normal.

Post-mortem notes. Surface of body. Skin of whole body, including extremities, covered with innumerable rounded, in some cases pedunculated soft tumours, varying in size from a pea to a small plum covered with normal skin and white on section. On the thighs and upper part of the legs small areas of coffee-coloured pigmentation. *Skeleton*, pronounced kyphosis. Left leg several inches shorter than right and outwardly rotated. At anatomical neck of left femur pseudo-arthrosis of comminuted fracture. Ribs retracted at attachment of diaphragm. Pelvic inlet heart-shaped.

Pelvic measurements.		*Average male.*	
Interspinous	25 c.c.	Interspinous	27·5 c.c.
Intercrystal	27 „	Intercrystal	30 „
Conjugate	7 „	Conjugate	12·75 „
Interacetabular	7 „	Interacetabular	12·75 „

Weight, 230 grammes.

All bones appeared very soft to the knife and on maceration porous (Fig. 1).

Thorax. Emphysema, apices of lungs adherent, purulent bronchitis both lower lobes.

Abdomen. Red granular kidney on each side. Gall-bladder contracted on to three mulberry-like calculi.

No obvious disease in remaining viscera.

For microscopic investigation pieces were taken from the vertebral bodies, ribs, and femur of all the cases, decalcified after fixation in 10 per cent. formalin with nitric acid, some incompletely, embedded in celloidin, and stained with haematoxylin and eosin and van Giesen. In order to arrive at a more certain conclusion as to the lime-salt content, especial value was placed upon an investigation of the frozen sections of the formalin-hardened material. In this way small sections were obtained sufficiently thin for the purpose. In Cases II, III,

and V the appearance of all the sections was normal. Sections of Case I showed the appearances detailed below; those of Case IV similar changes, but of a slight degree only.

(i) *Cross-sections of a rib, decalcified.* Apart from the periosteal changes to be described later, the appearances were characterized by an entire absence of marked abnormality in the general structure of the bone, in the arrangement of the bone-substance and marrow, and in the relative proportions of these two. This appearance, remarkable in view of the softness of the bone, was constant throughout all the sections of the ribs. The cortical substance consisted, as in the normal, of narrow Haversian spaces, nowhere dilated, and of Haversian systems. In these systems and also in the long trabeculae of the cancellous parts there was an entire absence of any other than lamellar formation. The marrow in the interstices consisted of lymphoid tissue with a moderate amount of fat, that is, of normal marrow. Enclosed linings of osteoblasts on the edges of Haversian canals were difficult to find, and still more difficult osteoclasts with Howship's lacunae (Fig. 3).

The above-mentioned periosteal changes consisted of a moderate and not very widespread formation of so-called periosteal osteophytes. These appeared as closely-packed outgrowths covered with a richly cellular periosteum, arcuate or hook-shaped on cross-section, characterized by their larger, rounder, and irregular bone-corpuscles.

(ii) *Haematoxylin and eosin sections of a rib not decalcified* presented a surprising picture, the greater part of the bone being devoid of lime-salts, i.e. osteoid. The pink staining in these sections brought out very clearly the arrangement of osteoid tissue around the centrally placed normal bone (see Fig. 4). These osteoid, i. e. osteomalacic, layers were present uniformly throughout the section in great thickness. In many places it was easy to see that the osteoid part was divided from the true bone by a sinuous border.

(iii) *Sections from undecalcified and decalcified vertebrae.* Briefly one can say that the picture presented by these sections corresponded closely to those described under (i) and (ii). In these also the decalcified sections looked practically normal. The compact bone with Haversian systems, as in the normal, formed but a small part, but it was equally noticeable, as in the former sections, that there was no widening of the Haversian canals. The cancellous bony trabeculae and marrow were present in the normal proportion and arrangement. Rows of osteoblasts and signs of lacunar resorption were as difficult to find as in the ribs. But again the quantity of osteoid tissue was surprising, being considerably in excess of the true bone.

(iv) *Sections from the compact and cancellous portions of the right femur, decalcified and undecalcified.* Once again there was a marked absence of any special histological changes in the decalcified sections. As in the normal, fat-marrow preponderated. Undecalcified sections were not so easy to prepare as from the previous bones; nevertheless, it could be quite clearly and definitely demonstrated that here also there was a large amount of osteoid tissue in

substantially the same arrangement as in (ii) and (iii). No signs of giant-cells or osteoblasts were detected.

In estimating the above-described changes and classifying them into one of the recognized varieties of bone disease, it is clearly only necessary to consider those which occur in adults and are accompanied by softening of the bone, that is to say, osteomalacia and osteitis fibrosa. It is well known that the chief characteristic of the latter is the replacement of the marrow by fibrous tissue. In the case under discussion there was no sign of this, and the question is at once narrowed down to a comparison with osteomalacia.

The microscopic pathology of osteomalacia has been the subject of considerable discussion, but such discussion has been chiefly as to the processes concerned rather than the appearances presented. It is agreed that a section of osteomalacic bone shows a layer of osteoid tissue of varying thickness covering the surface of the bony trabeculae, and lining the Haversian canals in contact everywhere with what remains of true bone. This is the fundamental histological change. With it there is stated also to occur, in advanced cases, dilatation of the Haversian canals, the conversion by resorption of compact bone into a spongy mass, and the appearance of osteoid trabeculae *de novo*, distinct from the deposit of osteoid on pre-existing bony ones. E. Kaufmann (5) states that the characteristic change in osteomalacia is a combined over-production and over-destruction of bone, the over-production resulting in practically lime-free tissue—osteoid—to an extent which appreciably increases the thickness of the bone, diminishing at the same time the marrow cavity; the over-destruction being responsible for the porous, spongy texture of the bone so formed.

It is clear that the appearances described in the above sections agree with those of osteomalacia in the presence and arrangement of osteoid tissue. But neither macroscopically nor microscopically was there evidence of any marked porosity, and certainly no sign of thickening or 'enostosis'. The porous character of the macerated pelvis (Fig. 1) is the result, not of a deficiency of bone, but of a deficiency of calcified bone, the osteoid tissue being all removed in the process of maceration. Prof. Ludwig Pick, laying great stress upon these two characteristics of osteomalacic bone, was of opinion that in this case it is a question of deficient calcification alone in an otherwise healthy bone, and that the process is a new one, distinct altogether from osteomalacia. With this I cannot agree, but hold rather that in these sections we have exactly the appearances described as characteristic of an average, that is, not very advanced, case of osteomalacia.

One such case, or at the most two, for in one other, as stated, similar osteoid formation was found to a less extent, cannot be made the basis for dogmatic statements, but it seems clear that in certain cases of von Recklinghausen's disease there occur changes in the bones macroscopically and microscopically resembling those of osteomalacia. The importance of this lies not in the mere addition of a symptom to a disease, but in the broadening of our conception of that disease, and the search for its cause.

Three main views have been advanced as to the cause of osteomalacia: (i) a disturbance of digestion which results in an excessive production of lactic acid; (ii) a microbic infection; (iii) a disturbance of the function of one or more of the glands of internal secretion.

The first of these remains a theory unsupported by definite evidence. As to the second, Morpurgo (9) states that he has isolated a diplococcus from the marrow of osteomalacic bones, and produced bone-changes in rats by injection of this organism. Other investigators have failed to isolate the organism, but Moussou and Charrin (10) have reproduced osteomalacia in pigs and rabbits by injections of osteomalacic marrow. There is, however, a mass of clinical and experimental evidence that the third view is not without foundation, although different observers consider different glands to be at fault. Thus removal of the ovaries in women suffering from osteomalacia is followed by arrest, if not improvement, of the disease. But the mere fact of its occurring in males also in a precisely similar form demonstrates that the ovaries, whilst no doubt concerned, cannot be the seat of the primary trouble. Pituitary extract has been tried as a therapeutic measure in osteomalacia, and three observers, Koch (6), Neu (8), and Bab (1), have reported good results. On the other hand, Hallion and Alquier (4) have produced in rabbits a softening of bone due to a simple decalcification by prolonged feeding upon powdered whole pituitary gland. Whilst speaking of the pituitary, it is interesting to note that a case of von Recklinghausen's disease, together with acromegaly, has been reported by Wolfsohn and Marcuse (12), and also by Frounard, and one of von Recklinghausen's and dystrophia adiposo-genitalis by Lier (7), which, if not mere coincidences, only serve to increase the confusion as to the possible rôle of this gland.

Finally, Erdheim (2) attributes osteomalacia and rickets to disease of the parathyroids, and states that he has found hyperplasia of these bodies in both diseases. Todyo (11) agrees with Erdheim that there exists a relation between the parathyroids and osteomalacia, but is unable to confirm the occurrence of hyperplasia in all cases and finds no correspondence between the degree of hyperplasia and the degree of osteomalacia.

In the cases whose skeletons I have examined an attempt was made to investigate the parathyroids and the hypophyses; the latter were found to be histologically normal; the former, owing to the method of preservation, were either not found, or found quite unfit for microscopic examination.

But it is clear that with osteomalacia established as a frequent symptom in the von Recklinghausen's complex, careful investigation of these glands is called for, to help to determine not only the cause of the osteomalacia, but its relation to the other symptoms, and the possible dependence of the disease as a whole upon a dystrophy of endocrine glands.

Conclusions.

1. Von Recklinghausen's disease is more than a disease of peripheral nerves and skin.

2. A frequent symptom is softening of the skeleton.

3. This softening is microscopically and macroscopically the same as osteomalacia.

4. Osteomalacia being probably a disease of the glands of internal secretion, these glands must be studied in von Recklinghausen's disease.

Notes of Remaining Cases.

Case II. F. G., married woman, aged 37. No history of skin disease in the family. Healthy till 15 years old, then measles, one year later typhoid. Since 1912 frequent attacks of heart trouble. But from 12 years onwards freckle-like spots which she had noticed all her childhood began to increase in size. Spots spread over whole body, increased steadily in size till death, and numerous small pedunculated tumours also appeared.

On admission, May 26, 1913, middle-sized, thin, miserable-looking woman, skin of whole body darkly pigmented, on trunk and arms numerous soft pedunculated fibro-lipomata of varying size.

No abnormality detected in skeleton.

Heart enlarged, sounds weak, action regular.

Died from heart failure on July 18, 1913.

Post-mortem notes. Pigmentation of skin and tumours as above. A few tumours on cutaneous nerves of right arm, chronic interstitial and parenchymatous nephritis.

Case III. H. L., workman, aged 22.

History. Admitted to hospital in 1913 for cough and slowly increasing swelling of the neck, for which he underwent an operation (?). Relieved until a few weeks previous to second admission, when he began to suffer from a return of cough and dyspnoea.

State on admission, Jan. 12, 1914. Patient thin, emaciated man, slightly cyanosed, suffering from dyspnoea. On left side of neck irregular firm tumour extending downwards behind under end of left clavicle. Complete paralysis of left vocal chord on laryngoscopic examination. X-ray examination revealed an abnormal shadow extending from lower jaw to arch of aorta.

Operation, Jan. 16. Excision of part of sternum and upper rib cartilage. Tumour proved inoperable. Pleura accidentally wounded. Patient died from empyema on Feb. 4.

Case proved to be a marked instance of von Recklinghausen's disease, with sarcomatous degeneration in a neurofibroma of left vagus nerve.

Skin of whole body covered with pigmented spots of varying size, but no tumours in the skin were found, but neurofibromata were found in considerable numbers along the following nerves:

The right obturator,
The right external cutaneous nerve of the thigh,
The left obturator nerve,
The left anterior crural nerve and its branches, and
The smaller branches of the left sciatic.

Tumours also on one or two intercostal nerves, the right ulnar, the left median, and the right cervical sympathetic.

The largest of these was the size of a goose's egg, that is, roughly a quarter the size of the sarcoma of the left vagus.

No skeletal changes.

Case IV. F. T., waitress, aged 46.

Previous history. 'Lung trouble' for three years. Since age of 20 had noticed skin nodules which had increased in number and size, a few being tender.

State on admission, Jan. 8, 1913. Multiple fibroma on chest, back, and abdomen, some pedunculated, a few tender. Advanced pulmonary and laryngeal tuberculosis.

X-ray report. No abnormality of shadow of pelvis, vertebrae, or long bones.

Death Feb. 21.

Post-mortem notes.

Externally. Extreme emaciation. Tumours from the size of a pin's head to a pea distributed widely over trunk and extremities. Punctate brown pigmentation of skin of chest and back of hands.

Internally. Tumours of small size along course of ulnar and median nerves, also on branches of sciatic and the cervical nerves on the right side. Sympathetic abdominal plexuses showed frequent varicosities.

Section of the ribs, vertebrae, femur, pelvis, and skull demonstrated very definite softening of the bone. No kyphosis or scoliosis, no deformity of pelvis. Advanced tubercular disease of lungs and larynx, isolated tubercles in kidneys.

Case V. E. K., female rent collector, aged 38.

Patient admitted suffering from pulmonary tuberculosis, June 3, 1914.

State on admission. Poorly developed woman, with marked scoliosis dating from a fall when 15 years old. Brunette skin covered with pigmented spots up to size of shilling. In addition, numerous sessile skin tumours, varying in size from pin's head to Tangerine orange.

Mental development poor.

Signs of active tuberculosis in both lungs.

Death from this condition on July 15, 1914.

Post-mortem notes. Body very emaciated, skin tumours and pigmentation as above.

Apart from deformity of ribs corresponding to scoliosis, no evidence of changes in bones.

A few tumours on terminal branches of nerves of the extremities only.

Advanced tuberculosis of lungs and larynx, also small intestine.

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DESCRIPTION OF FIGURES.

PLATE 14. FIG. 1. Photograph of pelvis of Case I, showing porous nature of bone and typical deformities of osteomalacia.

FIG. 2. Photograph of normal pelvis for comparison with above.

PLATE 15. FIG. 3. Section of decalcified rib from Case I, showing absence of marked change in general structure of bone.

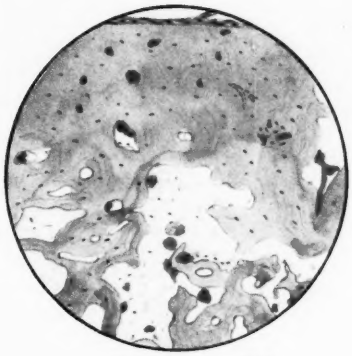
FIG. 4. Section of rib from Case I, not decalcified. Differential staining of bone (blue) and osteoid tissue (pink).



FIG. 1. Photograph of pelvis of Case I

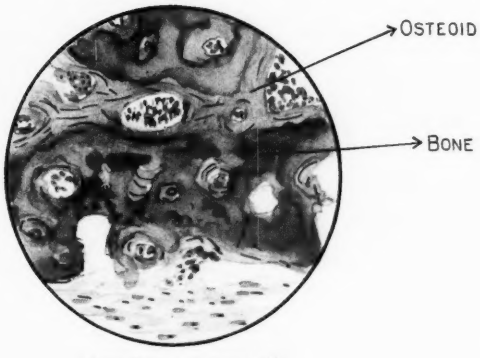


FIG. 2. Photograph of normal pelvis



DECALCIFIED $\frac{2}{3}$ RD
HÆMATOXYLIN AND EOSIN

FIG. 1.



NOT DECALCIFIED $\frac{2}{3}$ RD
HÆMATOXYLIN AND EOSIN

FIG. 2.

WAR NEPHRITIS

A CLINICAL, FUNCTIONAL, AND PATHOLOGICAL STUDY

By N. M. KEITH and W. W. D. THOMSON

(From a Research Laboratory at a Base Hospital in France)

A Report to the Medical Research Committee

With Plates 16–18

Owing to the comparative rarity of acute nephritis in civil practice few opportunities have been afforded for a study of renal function from the earliest stages of the disease. The occurrence of a large number of cases of this condition among our troops on active service presented, therefore, a unique occasion for its clinical, functional, and pathological study.

This investigation was carried out at a base hospital equipped with adequate laboratory facilities for this type of work. We had the additional advantage of being in charge of a ward specially reserved for cases of nephritis. Thus our laboratory work was never divorced from clinical observation. The data presented in this paper have been obtained from thirty-three cases specially selected from some three hundred which have passed through our hands. These were all typical cases of war nephritis, and, with one exception, only those were included which from their previous history and clinical condition negatived as far as possible a previous nephritic condition.

Plan of Investigation.

As long as the patient showed any oedema or other serious symptom he was kept on a regulated fluid diet of 2,200 c.c., of which 1,800 c.c. were milk. This diet contained from 2·5 to 3·0 grm. of chlorides as shown by analysis and about 12·0 grm. of nitrogen as estimated from tables. As the oedema cleared up and the general condition improved, bread and butter and milk puddings were added. Later on, chicken or fish, vegetables, and fruit were permitted. It was naturally impossible in a military hospital to keep this increased diet strictly uniform, but on an average it contained about 4 grm. of chlorides and about 15 grm. of nitrogen.

The daily output of urine was measured, its specific gravity taken, the total excretion of albumin calculated by Esbach's albuminometer, and the presence or absence of blood noted. At frequent intervals fresh specimens of urine were centrifugalized and the sediment examined in regard to its pathological contents.

Much time was devoted to the estimation, both in the blood and in the urine, of certain substances normally excreted by the kidney. Chief attention in this respect was given to urea and chlorides. In the blood we estimated the amount of urea and the total non-protein nitrogen and the chloride concentration of the plasma. The urea in the blood was estimated by Folin's modification of Marshall's urease method (1), the total non-protein nitrogen by Folin's micro-Kjeldahl method (2), and the plasma chlorides by the McLean-van Slyke method (3).

The urinary chlorides were estimated daily by Volhard's method. Towards the end of the patient's stay in hospital, and when the output of chlorides in his urine was regular, the patient was given a single additional 10 grm. of sodium chloride. The elimination of this extra salt and its effect on the chloride concentration of the urine and on the total quantity of urine passed was noted.

In certain cases daily estimations of the amount of urea excreted were made by Marshall's method (4). In addition, the urea in the urine was estimated at the same time as the urea in the blood, to obtain the necessary data for Ambard's coefficient (5) of urea excretion. The formula employed was:

$$\frac{Ur}{\sqrt{D \times \sqrt{\frac{C}{5}}}} = K.$$

Ur = grammes of urea per litre of blood.

D = „ „ excreted in twenty-four hours; calculated from excretion in one hour.

C = „ „ per litre of urine.

The excretory power of the kidney in eliminating a substance foreign to the organism was also studied. For this purpose we employed phenolsulphonephthalein, following the original technique of Rowntree and Geraghty (6) except that the injection was given intravenously instead of intramuscularly, so that the oedema often present in these cases should not interfere with the absorption of the dye.

In addition to the above purely functional tests of renal efficiency, repeated examinations were made as to the acid-base relationship in the blood. The subject was studied by three methods:

1. By the estimation of the alveolar carbon dioxide tension in the alveolar air by the method recently devised by Marriott (7).

2. By the estimation of the alkali reserve of the blood by the Rowntree-Marriott (8 and 9) collodion sac method.

3. By the estimation of the combined carbon dioxide of the plasma by van Slyke's (10) pipette.[1]

Classification of Cases.

As the investigation proceeded it became evident that, although the majority of the cases rapidly improved, yet a considerable proportion recovered very slowly from their initial symptoms and steadily tended towards chronicity. Hence two main groups, resolving and non-resolving, could be distinguished. Certain cases, however, lay on the border-line and tended to merge these two types into one another, thus preventing an absolute line of demarcation between the two.

Separate sections are devoted to the fatal cases and to those in which a relapse was the outstanding clinical feature. In another section, in addition and not included in our series, are discussed cases of acute nephritis following a definite focal infection which, differing in many respects from typical war nephritis, we have termed infective. This latter is the same form of acute nephritis which is often seen in civil life as a sequel to acute infections.

Resolving Group.

Twelve cases which presented similar clinical symptoms and functional disturbances were selected for special study (Table I). They arrived at the base five to thirteen days after onset and remained in the hospital for about one month. All had definite oedema of the face and lower back, while some in addition had swelling of the lower legs and signs of fluid in the chest cavity. On admission, dyspnoea was present in eight cases, being most marked in three which also had signs of bronchitis. Four, though still oedematous, were quite free from respiratory distress. The oedema cleared up rapidly, disappearing within ten to twenty-five days from onset. With the disappearance of oedema there was always a definite increase in the excretion of urine. In ten cases this pouring out of substances retained in the body was marked by a diuresis lasting for several days, while in two cases an increased elimination was indicated by a moderate polyuria persisting during the entire oedematous period. General clinical improvement was very noticeable with the onset of increased urine excretion. In ten cases systolic blood-pressure determinations, which before diuresis had ranged from 140 to 170 mm. Hg, showed a distinct fall after diuresis to 100–125 mm. Hg. In the remaining two the blood-pressure was within normal limits throughout. On ophthalmoscopic examination slight neuro-

[1] Normal functional values: A continued daily urinary output of 2,000 c.c. or over has been considered to constitute a diuresis. In the blood 45 mg. per 100 c.c. of urea and total non-protein nitrogen were fixed as the upper limits of normal. Normal figures for plasma chlorides, 560–620 mg. per 100 c.c.; Ambard's coefficient of urea excretion, 0·06–0·09; phthalein excretion, 60–75 per cent. in one hour; alveolar CO_2 tension, 38–45 mm. Hg; RpH, 8·3–8·5; and combined CO_2 in plasma, 55 to 78 c.c.

retinal oedema about the margin of the optic disk was found in four out of twelve cases, but lesions of a more severe type, such as haemorrhages and areas of degeneration, were never observed. The temperature rose to 99° or 100° in several cases without any determinable cause.

Routine urine examination. The specific gravity tended to be low during diuresis. However, following the output of retained fluid the urine concentration soon rose. This occurred in nine cases within four to five weeks from onset. In only three cases did it continue to remain as low as 1·010–1·013 from five to seven weeks after the beginning of the disease. The amount of albumin in the urine decreased as a rule with improvement in renal excretion. In one case the original amount, 0·1 per cent., persisted during the patient's entire stay in the ward. Generally the number of casts also diminished along with the decrease of albumin, but in three cases casts were just as numerous at the time of discharge as on admission. While macroscopic blood was observed in the urine of only three cases, yet red blood corpuscles were present microscopically in all cases. Polymorphonuclear leucocytes and large round mononuclear cells, often containing blood-pigment, were of frequent occurrence.

Functional studies. Renal functional tests were commenced within two weeks of initial symptoms and repeated several times during the stay in hospital. From the time of admission phenolsulphonephthalein was well excreted, the output varying from 40 to 66 per cent. One case admitted in convulsions excreted as low as 25 per cent., but a week later the figure stood at 60 per cent. The urea content of the blood was slightly raised in four cases, being 46–57 milligrammes per 100 c.c., but after diuresis it fell to normal. Accompanying this fall in blood-urea the total output of urea in the urine rose. In four other cases there was a corresponding decrease in the total non-protein nitrogen of the blood from 47–62 mg. per 100 c.c. to 27–39 mg. The amount of urea in the blood was quite normal in the remaining four cases during their entire stay in the hospital, and the total non-protein nitrogen determined in three of these was also normal. Estimation of the chlorides in the plasma showed a high initial amount in six cases, but following diuresis there was a gradual fall to normal. In three of the six cases during flood diuresis there was an early fall in the plasma chlorides with a moderate second rise when the amount of urine diminished. When oedema was present three cases had a normal plasma chloride content. During diuresis there was always a marked increase of the total chlorides in the urine, while in half the cases the chloride concentration was increased, resulting in what French workers term a chloride 'débâcle'. The disappearance of the oedema corresponded closely with the termination of high chloride excretion. The addition of 10 grm. of salt to the diet just before evacuation from the hospital gave the following results: four cases which had showed increased concentration of chlorides in the urine during diuresis excreted the extra salt by a rise in chloride concentration; five cases with an original normal concentration eliminated the extra salt either by diuresis or by an increase in concentration; the remaining three failed to excrete the extra salt satisfactorily,

although during diuresis the concentration had been good ; the onset of haematuria some time after the original diuresis was thought to bear some relationship to this later failure in chloride excretion.

Acid-base relationship. Early in the disease nine of the twelve cases had a definitely diminished alveolar CO_2 tension, ranging between 25 and 35 mm. Hg. In order to confirm this evidence of a mild degree of acidosis, the alkali reserve of the blood was determined by Marriott's method in three of these cases. The moderately reduced RpH of 7·9, 8·0, and 8·2 corresponded to the alveolar CO_2 tensions of 25, 33, and 35 mm. Hg. Simultaneous estimations of the combined CO_2 of the plasma and alveolar CO_2 tensions were also made in three others. Here again the alveolar CO_2 tensions of 32, 33, and 35 mm. Hg were associated with a condition of diminished alkali reserve in the blood—the combined CO_2 amounting to 40, 46, and 48 c.c. Following diuresis and general improvement, the three determinations indicated a rapid rise to the normal (see Table I). With one exception this restoration took place without the use of alkali therapy. On the other hand, one case, E. I., had no evidence of an acidosis previous to the onset of a marked diuresis nor during the subsequent course of the illness.

Non-resolving Group.

In a certain number of cases the delayed onset in general improvement and slow disappearance of oedema indicated a more severe type of renal disease than in the resolving type previously described. Ten cases of the present series belong to such a group (Table II). On admission, one to three weeks after reporting sick, all showed moderate or marked general oedema, complained of general weakness and lack of appetite, and in eight of the ten cases dyspnoea was present. On the routine diet and hot packs improvement was slow, and the diuresis which ensued so quickly under similar conditions in the resolving cases was delayed. Even when the increased urinary elimination did commence, as indicated by a distinct diuresis or intermittent polyuria, the oedema disappeared slowly and in several cases had not entirely resolved until a second diuresis had occurred. In the most protracted case of this type, W. V., oedema was still present at the end of three months. With this exception the last trace of oedema disappeared in two to seven weeks after onset as compared with one to three weeks in the resolving type. During recovery these patients were very susceptible to mild relapses, the occurrence and details of which are discussed below, and a secondary anaemia always developed while in the hospital. Three cases on admission had a systolic blood-pressure varying between 165 and 170 mm. Hg, which before evacuation had fallen to 120 mm. Hg. In four cases the blood-pressure varied between 90 and 140 mm. Hg during their stay in hospital. In three cases with long-persisting oedema the blood-pressure was quite normal throughout in two, while in a third, W. V., it continued to be high—160 to 200 mm. Hg up to the time of evacuation. Changes in the eye-grounds were fairly common, abnormalities being observed in six of the cases. Two had neuro-retinal oedema

only, two a few isolated haemorrhages, while two others developed both areas of degeneration and haemorrhages as the disease progressed. The development of these changes were of interest in W. V., the case with persistent oedema and high blood-pressure previously mentioned. On the seventeenth day of the disease the eye-grounds were normal. The next examination was made on the fiftieth day, when neuroretinal oedema, numerous haemorrhages, and one small pale area suggesting early degeneration were present. Later, on the ninetieth day, the eye-ground picture was quite typical of that so often seen in chronic nephritis—the whole disk margin being obscure and numerous haemorrhages and yellow areas being scattered everywhere throughout both retinae. Occasional rises of temperature to 99° and 100° occurred in all cases, but temperatures of 101° and 102° were only recorded with complications, as tonsillitis, phlebitis, and conditions simulating trench fever.

Well-marked blood changes may take place in this group. The haemoglobin was often reduced to 50 per cent. As the red blood corpuscles were not proportionately reduced, the colour index was below unity. Unless a secondary infection was present, there was no leucocytosis. Differential counts showed that the polymorphonuclear leucocytes were relatively reduced, while the large mononuclear hyaline cells were relatively increased.

Routine urine examination. The specific gravity was usually low during the period of diuresis or polyuria. Subsequently in half these cases the specific gravity remained at 1·013 to 1·017 until discharge; on the other hand, in five cases it tended to fall and become fixed at 1·010 to 1·012 regardless of the daily amount of urine excreted. This continued inability to eliminate a urine of normal concentration suggests permanent renal damage. The amount of albumin in the urine decreased in nine cases, though on discharge the amount varied between a trace and 1·2 per cent. In one case it remained stationary at 0·7 per cent. throughout. This diminution in the albumin usually coincided with improved renal function, but in several instances a small amount of albumin was accompanied by a poor excretory ability. The periodic appearance of gross blood in the urine was typical of these cases. Macroscopic haematuria was more or less persistent in six cases; its presence was not incompatible with moderately good renal function. With the appearance of gross blood there was an apparent decrease in the number of casts. This decrease was more apparent than real, as on laking the red blood corpuscles many casts could be observed in fields where previously none had been seen, the red cells having overlain and hidden the casts. It was remarkable that with marked haematuria blood-casts were very rare. On macroscopic examination red blood corpuscles, polymorphonuclear leucocytes, and large mononuclear cells often containing blood-pigment were found in all of these cases. The presence of microscopic pus definitely arising from the kidney itself was demonstrated in one case by means of ureteral catheterization.

Functional studies. More marked and varied changes were revealed in these cases than in the resolving group. Distinct fluctuations in the ability of the kidney to excrete phenolsulphonephthalein, urea, and chlorides were

characteristic, though very often one substance might be very well eliminated whilst another was retarded. In Table II these variations are given in detail. All of the ten cases at some period while under observation showed a diminished phthalein excretion—the amount varying from 10 to 50 per cent. Two cases, which on admission excreted 32 to 38 per cent., gradually improved and before evacuation had an output of 62 to 64 per cent. Two, more serious cases, showed weekly fluctuations, but on discharge eliminated only 18 to 22 per cent. On the other hand, in five cases with an initial excretion of 45 to 55 per cent. there was a tendency for the excretion to remain at this level or decrease slightly with apparent general recovery. The urea content of the blood was definitely increased, 77–158 mg. per 100 c.c., in seven of the ten cases, while in an eighth patient a total non-protein nitrogen of 87 mg. indicated a heightened blood-urea content. In two cases the blood-urea content was within normal limits during the patient's stay in hospital. This increase in the urea in the blood was more marked and occurred in a much higher percentage of cases than in the previous type. The blood-urea was found increased more frequently in the early stages of the disease, though a high blood-urea content was not limited to any particular period. When the total non-protein nitrogen was determined on the same specimen of blood in these cases of retained urea, the urea nitrogen averaged 63 per cent., but when, on the other hand, the total urea was within normal limits, the urea nitrogen averaged 48 per cent. Ambard's coefficient was determined at different periods in eight of these cases, and in every case the resulting index was above the normal. On discharge, in four cases Ambard's coefficient varied between 0·098 and 0·165.

The concentration of chlorides in the plasma was initially high in six cases, and subsequent estimations revealed results similar to those in the resolving group. In two cases the chlorides gradually fell to normal, while in the other four there was a decrease during or immediately after diuresis, with a later rise and a final fall to the normal level. The plasma chloride content was normal or only slightly elevated in one case during his stay of seven weeks in the ward. In an eighth case the chloride content was normal on admission, but later became high and remained so until discharge. This was associated with a low chloride concentration in the urine. The most interesting case in this series with regard to chloride metabolism was W. V. On admission the plasma chlorides amounted to 624 mg. per 100 c.c. During the next three weeks the oedema increased, water and chlorides were excreted in small amounts, and at the end of this period the chlorides in the plasma had reached the low figure of 490 mg. per 100 c.c. Later, following an increased elimination of chlorides and water in the urine, the plasma chloride content rose to 600 mg. per 100 c.c. Thus a marked retention of chlorides in the tissues was associated with a plasma chloride content 12 per cent. below the generally accepted threshold.

The excretion of chlorides in the urine was often diminished, as one might expect from the slow disappearance of oedema and tardy onset of increased urinary output. Early in the disease four cases had both a low concentration

and a low total output, although the plasma chlorides were above the threshold. With improvement in clinical condition and renal function, the chlorides were well excreted. Three of these cases were given the sodium chloride test before discharge—one excreted the extra chloride exceedingly well, while the other two had a fair concentration, but failed to eliminate the total quantity. In four cases the chloride concentration and total output were normal throughout their stay in hospital, and the final extra salt was well excreted with the exception of one case. The remaining two cases, S. H. and J. K., showed fluctuations in all excretory functions, including the chlorides. These changes were due to mild relapses. Both these cases failed to excrete satisfactorily the additional chloride given before discharge.

Acid-base relationship. There was evidence of a diminished alkaline reserve in nine of the ten cases. In all probability the remaining case, W. V., would have shown a similar condition, but alkali had been administered shortly after his admission to the casualty clearing station and subsequently while at the base. The alkali reserve of the plasma was estimated in a number of these nine cases on a specimen of the blood taken at the same time as the alveolar CO_2 tension was determined. For convenience the results obtained will be described together. On admission, in all of the nine cases, the alveolar CO_2 tension varied between 23 and 35 mm. Hg; in five the RpH between 7·8 and 8·2, and in four the combined CO_2 was 37 to 47 c.c. Thus it will be seen that the initial acidosis in these cases, though still moderate in degree, tended to be slightly more marked than in the resolving group. Two cases only, J. T. and H. W., recovered rapidly without therapy. Two further cases were not given alkali for some time after admission, and a deficiency of alkali reserve persisted. On the other hand, in two other cases alkali was administered early, and within a few days the acid-base relationship became normal, but subsequently, after discontinuing the medication, relapse occurred and the acidosis reappeared. These cases were then given alkali till discharge. Having observed this tendency of the acidosis to persist and also recur, alkalies were given from admission till evacuation in three cases and no return of the condition was manifest. The effect of alkali thereby on the acid-base equilibrium in certain of these cases is tabulated below.

Name.	Date.	Alkali Medication.	Alveolar CO_2 Tension mm. Hg.	RpH.	Combined CO_2 c.c.
A. S.	11/iv	None	25		
	3/v	None	25	8·1	
	6/v	Sodium lactate grm. 4, four-hourly			
	24/v	" "	35		
J. K.	2/v	" "	25	7·8	
	12/v	" "	38	8·2	
	27/vi	Discontinued			
	16/vii	Relapse	28	8·1	39
	16/vii	Sodium bicarbonate grm. 4, four-hourly			
	23/vii	" "	40	8·3	73
W. G.	23/viii	" "	28	7·9	37
	28/viii	" "			
	4/ix	" "	39		59
	3/x	" "	43		59

Relapses.

Cases of war nephritis show a tendency to relapse. In this series eight or over 24 per cent. had severe exacerbations of the disease. Often a definite cause, such as an intercurrent infection, was present, but sometimes no causative factor could be demonstrated. We do not include as relapses those frequent recrudescences, marked by a slight fever and by increased blood and albumin in urine, which last only a few days and leave the patient, as far as functional tests show, none the worse.

In two of the eight cases (S. H. and J. K., Table II) the relapse prolonged the ordinary course of the disease. These cases have already been referred to in the non-resolving group. In six the relapse was much more severe than the original attack and caused symptoms so grave that the patients' lives hung in the balance—of these two died and four recovered. It is with the course of these latter four that this section specially deals (Table III).

These four cases arrived at the base on the fourth to the ninth day of illness. All showed moderate signs of bronchitis, only one had a phthalein excretion below 50 per cent. For varying periods after admission progress was excellent. The usual diuresis took place with an accompanying flood of chlorides and disappearance of oedema. In every case the phthalein excretion rose to 60 per cent. or higher. In no way did their course differ from that of other members of the resolving group, and a speedy recovery was anticipated in each case. Unfortunately, however, in periods ranging from the fourteenth to the twenty-first day of disease each had a severe relapse. This relapse was heralded in each case by a smart rise in temperature to 100°–103·4° F., by the appearance of gross blood in the urine, by a fall in the urinary output, and a return of tenderness on pressure over the costo-vertebral angles. In one case, W., the relapse was due to a staphylococcal epididymitis. This patient gave an indefinite history of venereal infection three years previously. Ten days before the epididymitis developed a urethral discharge had been noticed and his urine became very rich in pus cells. No gonococci could be found and Wassermann's reaction was negative. A second case, E., developed, during the relapse, a phlebitis. In the third case, C., the relapse was attended with severe pains in the shins and ankles, simulating an attack of trench fever. In the fourth case, B., no cause could be found for the relapse.

The urinary output kept low for periods varying from four to thirteen days, but only in one case, C., did the daily amount fall below 500 c.c. In this case the output averaged 300 c.c. per diem for ten days, falling as low as 150 c.c. With this retention of water, in two cases only did oedema reappear. This amounted at most to a spongy pad over the sacrum, and never at all simulated the original condition. Although in all these cases there was a marked urea retention, yet in only two, C. and B., did we observe any so-called uraemic symptoms. These patients had at times severe headache, some vomiting and vertigo, but never were convulsions or muscular twitchings observed. In the

other cases subjective symptoms were strangely absent, at most slight headache and some distaste for food. In no case was there a return of the distressing dyspnoea. An interesting clinical feature of these cases during relapse was a fall of systolic blood-pressure from 130–150 to 95–115 mm. Hg. One case, C., developed during relapse two small retinal haemorrhages. No eye-ground changes were observed in the others.

Routine urine examination. With the relapse there was always a sharp fall in the amount of urine. The urine was coloured dark red with blood. This gross haematuria lasted from one to seven weeks. In the case, B., in which the colour of the urine cleared in a week, the haematuria returned at intervals.

In two cases (C. and W.) the specific gravity showed a marked rise as the quantity of the urine fell. When diuresis was established the specific gravity fell and remained at a low level till evacuation from hospital. In one case (E.) the specific gravity steadily fell and remained low; the urinary output in this case had never fallen below a litre and the diminution was transient. The specific gravity of the fourth case (B.) did not vary. The amount of albumin always showed a rise at the beginning of the relapse; but if the urine output continued low there was a secondary fall.

Functional studies. An absolutely constant finding was a very sudden drop, not only in the total output of chlorides but also in the chloride concentration of the urine. This fall accompanied the decrease in the amount of urine. In two cases (C. and W.), the day previous to the relapse, and while the output of urine was still at a high level, there was a sharp rise in chloride concentration in the urine. This preliminary rise previous to a drop was noticed several times in other cases of milder relapses. Long after the amount of urine had risen to its original level this low chloride concentration continued, and lasted for periods ranging from four to seven weeks, and in one case (E.) was still low when the patient left hospital eight weeks later. Thus no avalanche of chlorides, so striking a feature in the non-resolving group, followed the re-establishment of urinary output after a relapse. The response to the extra salt test was a sharp rise in three cases of the chloride concentration of the urine and the extra salt was well eliminated. The fourth case (E.), whose chloride concentration in the urine had remained persistently low since relapse, failed to eliminate the additional salt.

In only one case (C.) did we closely follow the excretion of urea. This remained at a low total during the period of low urinary output, but the concentration kept at a fair level. With the establishment of diuresis the total excretion of urea rose *pari passu* with the excretion of water.

Before the relapse all four cases were excreting 60 per cent. or over of phthalein. In two (C. and B.) it fell at once to a mere trace, not estimable; in a third (E.) to 20 per cent. and later to 14 per cent. In the fourth case (W.) the fall was slower, at once to 50 per cent., and a week later the figure was still further reduced to 33 per cent. This case a month later had again risen to 60 per cent., while the other three were still under 40 per cent. on departure from hospital, six weeks to two months after the relapse.

In all four cases there was a marked retention of urea, the urea content of the blood varying from 93 to 220 mg. per 100 c.c. of blood. The highest blood urea content was reached in from six to seventeen days after relapse, and the fall to normal was much more gradual, taking from eighteen to fifty days. One case (E.) still showed a figure of 56 mg. per 100 c.c., with an Ambard's coefficient of 0·124, on leaving hospital seven weeks after relapse; while C., although blood urea was within normal limits, still showed an Ambard's coefficient of 0·116 on evacuation.

In only one of these cases during relapse did the plasma chloride content deviate from the normal figure. This was in Case C., in which a low urinary output had lasted for thirteen days. Here the plasma chloride content fell from 631 mg. per 100 c.c. to 418 mg., but with the establishment of a diuresis it rose quickly again to 612 mg.

Acid-base relationship. During relapse two cases received sodium bicarbonate, 4 grm. every four hours, with the result that little tendency towards acidosis was manifested. For example, C. in the third day of his relapse had an alveolar CO_2 tension of 39 mm. Hg. and RpH 8·4, and on recovery from relapse the figures were 42 and 8·4. On the other hand, two cases did not receive alkaline medication, with the result that during relapse distinct evidence of an acidosis developed; Case B. showing an alveolar CO_2 tension of 28 mm. Hg. and an RpH value of 7·9; Case W., alveolar CO_2 tension 33, RpH 7·9, combined CO_2 39 c.c. In both cases acidosis disappeared, in one with and in the other without the assistance of alkali therapy.

Acute Infective Nephritis.

In the mode of onset, development, and further course, two cases of acute nephritis resembled closely an acute infection. Both were young soldiers, aged 19 and 24, who reported sick with a definite localized infection, one with an otitis media involving the mastoid, the other with a diffuse infection of the right foot. A week to ten days later symptoms of nephritis were present. Operative treatment was instituted after the nephritis had developed, and in spite of good drainage and improvement in the local condition, high temperature and severe headache continued for two to three weeks. Following operation both cases were transferred to the nephritis ward and renal functional studies were commenced. Subjectively headache, fever, and costo-vertebral tenderness were the chief complaints. Oedema was very slight and limited to the face. Dyspnoea was not present. The disappearance of the oedema within a few days was not associated with a definite diuresis. The blood-pressure remained low—100 to 110 mm. Hg during the period of high fever, rising to normal with convalescence. The eye-grounds were normal in one case, while the optic neuritis, noted in the case of otitis media, L., was considered to be due to increased intracranial pressure.

Routine urine examination. The specific gravity ranged in one case

between 1·010 and 1·016 throughout. In another the specific gravity averaged 1·010 during the fever period, but later at the end of a month reached 1·014. Albumin was present in moderate amount, but decreased rapidly from 0·12 per cent. to a trace. Macroscopic blood was present during the fever period along with white blood corpuscles, large mononuclear cells, and numerous casts. With general improvement the casts became scanty, but red blood corpuscles and the large mononuclear cells still persisted.

Functional studies. The excretion of phenolsulphonephthalein was definitely diminished, being as low as 40 per cent. in both cases, and on discharge amounted to 45–50 per cent. The most striking functional disturbance was the high urea content in the blood, reaching 109 and 154 mg. per 100 c.c. with a corresponding increase in the total non-protein nitrogen. That this increase of urea in the blood was largely due to insufficient elimination was clearly indicated in one case by a high Ambard coefficient of 0·478. With the fall in temperature and general clinical improvement the blood urea rapidly fell to normal, although the phthalein output was still somewhat reduced, 45–50 per cent. In the case associated with otitis media Ambard's coefficient was normal, 0·075, before discharge. The chlorides in the plasma amounted in one case to 639 mg. per 100 c.c., but otherwise showed nothing abnormal. In the urine the chloride concentration remained low during the fever period, while on discharge the extra chloride was well eliminated.

Acid-base relationship. A slight but definite degree of acidosis was demonstrated in one of the two cases as shown by an alveolar CO_2 tension of 28 mm. Hg. Plasma withdrawn at the same time showed a slight reduction in the alkali reserve, RpH being 8·1, and combined CO_2 49 c.c. With improvement in the patient's clinical condition the acidosis quickly cleared up.

Fatal Cases.

The results of clinical and functional studies carried out on seven cases which subsequently died are given in Table IV, while detailed pathological findings in six of these cases are described below. One case was evacuated to England ten days before death, and during this latter period was under careful observation in St. Bartholomew's Hospital, London.[2] These patients varied in age from 22 to 33 years, and as far as could be ascertained were all in robust health before the onset of acute nephritis.

Two of these cases ended fatally at the end of the second week from onset. Both had moderate general oedema, a raised blood-pressure, and passed a urine of specific gravity of 1·020 containing a heavy cloud of albumin and many casts, white and red blood corpuscles, but no gross blood. Complete functional studies were not made because at that time we had not procured all the necessary laboratory equipment. Patient J. G. was admitted on the seventh day of

[2] We are indebted to Lt.-Col. J. Calvert for the notes and chart of this patient while under his care.

disease and appeared to be progressing satisfactorily; for four days his daily urinary output varied between 1,600 and 2,200 c.c. on a fluid intake of 2 litres, and during this period 50 per cent. of phthalein was excreted in one hour. Forty-eight hours before death he began to vomit frequently, and on the following day had repeated severe general convulsions. He remained in a comatose convulsive state till death. Respiration during the last twenty-four hours was deep, laboured, but regular, and the temperature did not rise above 100°. Patient P. R. was admitted somewhat later in the disease—the twelfth day—and soon severe vomiting along with Cheyne-Stokes respiration developed. At this time the alveolar CO_2 tension was 25 mm. Hg. Later, convulsions developed, and coma persisted till death on the fourteenth day. A few hours before death the phthalein excretion amounted to 10 per cent.

An infective process in addition to the original nephritis appeared to be the immediate cause of death in two cases, R. B. and C. M., on the thirty-fourth and seventeenth day of illness respectively. In spite of the continued oedema the output of urine was considerable, and the chloride concentration fair up to the time when phlebitis and staphylococcal septicaemia respectively developed. Renal excretion rapidly diminished as the infective process progressed, and in a few days the patient succumbed. During this latter period vomiting, severe headache, and mild delirium were present, but no convulsions. Both cases showed a high degree of urea retention. Acidosis was moderate in degree. One case failed to excrete phthalein.[3] Both of these cases showed retinal haemorrhages, and one an area of degeneration without any abnormality being noted in the optic disk or its margin.

Three cases with severe symptoms on admission and showing little or no improvement when subjected to the routine therapeutic measures were non-resolving in type. Unlike the favourable cases that later recovered, the oedema persisted, general anasarca gradually became more marked, and a diuresis or polyuria did not develop. The course of the disease, forty-five and fifty-two days respectively, was characterized by a gradual rather than a sudden decrease in renal function. The blood-pressure was initially raised, but fell with the development of terminal symptoms. Retinal changes were limited to several small haemorrhages in two of the cases. From the time of admission the excretion of phthalein was very small, a trace to 5 per cent. The total output of chlorides was low, and the urea in the blood high (indicated in two cases by increased total non-protein nitrogen). An acidosis accompanied these indications of severe renal insufficiency. The relationship between the chloride concentration in the plasma and urine was of particular interest as the disease progressed. In Case F. G. the initially high plasma chloride content decreased during the terminal period, but never fell below the normal threshold of 560 mg. per 100 c.c., while the concentration in the urine continued to be relatively high. On the other hand, in two cases the plasma chlorides fell to

[3] A phthalein test was not carried out in Case C. M. on account of the difficulty in catheterization due to a prostatic abscess.

a figure well below the normal threshold, and at the same time the chloride concentration of the urine became extremely low.

The terminal stages of the disease were marked clinically by oliguria, headache, vomiting, orthopnoea, bradycardia (in two cases), muscular twitchings, and final coma. In addition to these symptoms, B. had a single general convulsion. The respirations were always rapid, laboured, irregular at times, but the Cheyne-Stokes periodic type was not observed. There was no definite terminal rise in temperature, and the slow heart rate, thirty-two to the minute in F. G. a few hours before death, was striking. Complete anuria was never present, even post mortem the bladder always containing 100 c.c. or more of urine.

Pathology.

Our pathological data were obtained from six fatal cases whose clinical and functional histories have been already described. Of these two died in the second week and two in the seventh week of the disease. In two death was due to an intercurrent infection.

The two acute cases died on the thirteenth and fourteenth days respectively of illness. Histological examination showed features so similar to those described by Dunn and McNee (11) in a recent article that a detailed description need not be given here. Briefly the most important changes (Figs. 1 and 7) are enlargement and swelling of the glomeruli with marked increase in the nuclear elements. Nuclei in the process of mitotic division are not uncommon. Protrusions from these swollen glomeruli into the aperture of the proximal convoluted tubule are frequently seen. There is a marked absence of red blood corpuscles in the capillaries of the Malpighian tuft due to the blockage of these vessels by an accumulation of large mononuclear cells. Catarrhal changes and hyaline droplets are present in the epithelium of the convoluted tubules, while the epithelium of the collecting tubules shows less damage. Hyaline casts, numerous in one case, are found in the junctional tubules. In the second case casts are only found with difficulty. Intratubular haemorrhage is marked in both cases in the tubules adjacent to the arteriolae rectae. The interstitial tissue is not increased in amount.

Both of the fatal cases in the non-resolving group were young men of 22 and 26 years of age, and death occurred on the forty-fifth and fifty-second day of illness. Post-mortem examination showed the following naked eye appearances. Anasarca is general and the pleural and peritoneal cavities contain a large excess of fluid. The fluid in the pericardial sac in one case is not increased. The kidneys are enlarged, weighing from 225 to 260 grm. each.

The capsule still strips readily. Subcapsular mottling is very marked. Fresh bright red and older purpuric spots of haemorrhage are intermingled with pale areas of degeneration. On section the cortex is bulging and swollen, paler and duller than usual, and mottled. Standing out as white translucent glistening dots the glomeruli at once attract attention. The course of the straight

vessels is rendered very distinct owing to their congestion. The beefy tint of the pyramids contrasts strongly with the pallor of the cortex.

The heart is dilated but not hypertrophied. A few petechiae are present in one case under the endocardium of the left ventricle.

The lungs are voluminous, markedly congested, and oedematous. In one a definite area of red hepatization is present in the left upper lobe.

The liver is enlarged and congested. In one instance pale areas are scattered throughout the liver substance. These histologically proved to be areas of polymorphonuclear infiltration around the intralobular veins.

In one case the spleen is slightly enlarged, in the other it is markedly atrophic. In both subcapsular haemorrhages are present. Haemorrhagic areas are present in one case in the caecum. The haemolymph glands of the abdomen in one case are universally enlarged and bright pink in colour. The suprarenal capsules and pancreas show no gross change. The brain is oedematous, but in neither case are haemorrhages observed.

The histological changes (Figs. 3, 5, and 9) in these two kidneys are similar and in their evident character in sharp contradistinction to the acute cases. The majority of the glomeruli show an extensive and progressive proliferation of the endothelial cells lining Bowman's capsule. This results in a laminated thickening gradually filling up the lumen. Generally this thickening is arranged as a crescent with the horns pointing towards the pedicle of the tuft and the thickest part occluding the aperture of the convoluted tubule. Around the glomeruli there is a marked increase in connective tissue formation, and fine fibrils of fibrous tissue can be traced radiating outwards between the adjoining tubules, or passing inwards through the pedicle into the tuft. The tuft itself shows thickening of the walls of its capillaries with marked fibrous change in the supporting connective tissue. Adhesions take place between this altered tuft and the thickened capsule; these adhesions, together with the contraction of the fibrous tissue in the tuft, produce marked lobulation. All stages in this destruction of the glomeruli can be seen up to complete sclerosis. There is a very definite overgrowth of the interstitial tissue. This is especially marked in the cortex around the glomeruli and blood-vessels, where small round-celled infiltration is also evident. The connective tissue often runs in definite strands. The increase is much less marked in the pyramids where the interstitial tissue is much less dense and markedly oedematous.

Degeneration of the tubular epithelium is widespread and severe in degree. Some tubules are obstructed by the overgrowth of connective tissue; others are widely dilated and oedematous. The cells are swollen, irregular in outline, with faintly staining nuclei. Hyaline droplets in the cells of the convoluted tubules are of frequent occurrence. Sections of the walls of the tubules are often denuded of epithelium and the degenerated cells lie loose in the lumen. In one case haemosiderin is present in many of the epithelial cells of the convoluted tubules. Many of the tubules are filled with strongly eosin-staining hyaline material, and others contain granular débris in which are embedded

the remains of degenerated nuclei. Intratubular haemorrhage is a very striking feature and polymorphonuclear leococytes are of not infrequent occurrence. Many tubules contain the large mononuclear cells whose presence in the urine is so striking. These cells correspond histologically with the large mononuclear cells seen plugging the capillaries of the Malpighian tuft in the early cases as described above. The origin of these cells is doubtful, but we are inclined to regard them with Mallory (12) as being the large mononuclear leucocytes, or, as he prefers to call them, endothelial leucocytes, and are probably derived from proliferation and desquamation of the endothelial cells lining the capillaries. It is interesting to note in this connexion that, as already described, we have seen a relative increase of the large mononuclear leucocytes in the blood in the non-resolving group.

One of the two fatal cases whose death was due to an intercurrent infection was a non-resolving case who died on the thirty-fourth day of illness. This case (R. B., Table IV) had been making good progress clinically until he developed a phlebitis of his left median basilic vein. Gross pathological changes were very similar to those above described, but the kidneys were larger and softer. Bacteriological examination of the thrombus post mortem gave negative results. Histologically (Figs. 2 and 4) this kidney showed features intermediate between the early and late types detailed above. The glomeruli are now somewhat shrunken, and marked fibrous thickening has taken place in the supporting tissue of the capillaries, especially in the pedicle. Contraction of this tissue has produced distinct lobulation of the tuft. The accumulation of mononuclear cells is not so marked in the capillaries. The cells lining Bowman's capsule show proliferation of their nuclei, but only in a few glomeruli could distinct lamination be seen. The tubules are separated by a large amount of young and very oedematous connective tissue. The epithelium of the convoluted tubules is uniformly flattened. Casts, blood, and mononuclear cells in large numbers, are present in many of the tubules. There is a very marked small round-celled infiltration of the interstitial tissue, especially around the glomeruli and blood-vessels.

The second fatal relapsing case (C. M.), whose death was due to a staphylococcal septicaemia originating from a prostatic abscess, died on the seventeenth day of illness. The gross appearance of the kidney is similar to that described above, except that the cortex is darker and a few small pyaemic areas are present along the course of the vessels in the cortex. The two kidneys together weigh 585 grm. Histologically (Fig. 6) sections show, in addition to the features seen in the acute type, a marked exudation of blood and polymorphonuclear leucocytes into Bowman's capsule. The resulting fibrin forms a thick layer inside Bowman's capsule, and can often be seen plugging the neck and extending some way into the proximal convoluted tubule. This is accompanied by proliferation and desquamation of the capsular endothelium. All the blood-vessels are widely dilated and congested with blood. The tubules contain much blood and many polymorphonuclear leucocytes. Hyaline and granular casts

are fairly numerous. Mononuclear cells are rare. The lining cells of the tubules show marked cloudy swelling and hyaline droplet formation. The interstitial tissue is markedly oedematous and infiltrated with polymorphonuclear leucocytes.

We have had the opportunity of examining the kidneys of a case (J. D.) which died on the thirty-first day of the disease. This case was under the charge of Capt. J. M. McCloy and is not included in our series. The course of the disease was steadily downward and was not complicated by any intercurrent infection. The kidneys are soft, friable, and greatly enlarged, weighing together 620 grm. Apart from their large size and consistency, naked-eye appearances are similar to those described in the cases dying later in the disease. Histologically sections closely resemble those of R. B., already described, except that the glomeruli are not shrunken and lobulation has not taken place (Fig. 8). Proliferation and desquamation of the cells lining Bowman's capsule are present. In many glomeruli this only amounts to a multiplication of the nuclei. Crescent formation has not taken place. The increased size of the kidneys is due to the intense interstitial oedema. Small round-celled infiltration is present around the glomeruli and blood-vessels. The epithelium of the convoluted tubules is uniformly flattened and mitotic division of their nuclei is not uncommon. These two cases (R. B. and J. D.) show in every respect an intermediate stage in the progress of renal change between the cases dying in the second week of the disease and those in which death was delayed until towards the end of the second month.

In none of the cases described above did we find any histological evidence pointing to a previous renal lesion.

Prognosis.

In discussing the further course of these cases it must be remembered that this series was specially selected from the severest cases entering our ward. In general, the cases of the resolving type progressed satisfactorily while at the base. On evacuation they were free from oedema, had a normal blood-pressure, and good renal function, although albumin and cylindruria were still present. Subsequent reports from medical officers in England showed that recovery was slow—all the cases were still in hospital from two to four months after onset. Three cases were discharged within four months fit for further service. The only patient included in the series who had a previous attack of war nephritis ran a very favourable course, and at the end of three months his urine was free of albumin. It is interesting to note that this is one of the three cases so far reported to us in which the albumin had cleared up. Such facts would indicate that even with early satisfactory progress, prognosis as to final recovery must be guarded.

As was to be expected from the protracted early course of the non-resolving cases, recovery was delayed. Though nine out of the ten patients on evacuation

were oedema free and had a normal blood-pressure, none of them had strictly normal renal function. There was always a definite secondary anaemia, a tendency to periodic haematuria, and later, in England, the oedema reappeared in the dependent parts when the patients were allowed to walk. All of the non-resolving cases were still in military hospitals four to seven months after onset.

As previously mentioned, the occurrence of a relapse was of serious import. In the subsequent course of the four cases studied the condition improved slowly and resembled closely that seen in the non-resolving type. One case remained in hospital for nine months. We have no record of any of these non-resolving and relapsing cases being discharged fit for even light duty.

Our fatal cases represented a total mortality of 2·3 per cent. in 300 cases. Death may occur at any stage. In the early course of the disease fatal symptoms may arise suddenly, unforeshadowed by any marked derangement of kidney function. However, in the non-resolving group, grossly impaired function of a progressive nature may herald a fatal prognosis several weeks before death, recalling the slow and lingering termination of the chronic nephritic. Intercurrent infection at any time during the course of the disease was always of serious prognostic significance.

Treatment.

In the early stages of the disease the patients were given a milk diet restricted to 1,800 c.c. Though this was not a strictly low protein diet, no increase in the blood-nitrogen was observed to follow its use. Of more importance from a dietetic point of view was the limited intake of fluid and chlorides while oedema was present, owing to a retention of these substances in the body. In severe cases the oedema definitely increased in spite of the low intake. Von Noorden (13) has emphasized that in acute nephritis it is quite useless to give the patient large quantities of fluid in order to flush out the kidneys, as this only unnecessarily irritates an organ which is already incapable of excreting water. Widal and Lemierre (14) have shown how the administration or suppression of salt in the diet could determine the appearance or disappearance of oedema. After the retained substances had been excreted a more liberal diet, containing 4 grm. of chloride and 15 grm. of nitrogen, was permitted. No untoward results were observed to follow this increase in diet.

Because of MacNider's (15) demonstration that the administration of alkalies previous to the production of experimental uranium nephritis lessened the extent of the renal lesion, and also because a mild acidosis was present in many of these cases, alkali therapy was given a rather extensive trial. Three cases which did not seem to be progressing satisfactorily showed distinct improvement in renal function after the giving of alkali, sodium bicarbonate or sodium lactate, 4 grm. every four hours, for a period of seven to ten days. On the other hand, cases which received no alkali did extremely well. Again, several

cases received alkali in the above amounts for weeks, but showed no definite improvement. One case (C., Table III) was given bicarbonate previous to and during a serious relapse without apparent effect. That a diminished alkali reserve could be quickly restored by the use of alkali was strikingly demonstrated in the fatal case J. B. (Table IV). On admission the combined CO_2 of the plasma was distinctly decreased. With the administration of sodium bicarbonate, 4 grm. every four hours, the reserve of the blood became normal and the urine alkaline within four days. This condition was maintained throughout the remainder of his illness without any evident beneficial effect on the symptoms or course of the disease. 20 grm. of bicarbonate in 5 per cent. solution injected intravenously in three cases of oliguria failed to produce an increase in the urinary output. Persistent oliguria proved to be a serious therapeutic problem in six cases. 350 c.c. of 5 per cent. glucose given intravenously failed to increase the amount of urine. A negative result likewise followed the use of a 10 per cent. solution in a second case. Theobromine (0·5 grm. every eight hours for four doses) was employed in four of these cases. In one an immediate and persistent diuresis followed the use of this drug, while in the others no benefit was observed. For the treatment of convulsions, morphia, venesection, and lumbar puncture all appeared to be helpful, although in three cases, subsequently fatal, none of these measures had more than a temporary effect. Hot packs were employed as a routine measure in all cases of persistent oedema; of their utility, however, little evidence was obtained.

Discussion.

The term war nephritis has been employed to include several forms of renal disease. In the present investigation the term has been limited to those acute cases which showed an abrupt onset with symptoms of dyspnoea and oedema. We have described a so-called infective acute nephritis, which from the mode of onset and general course would appear to be quite distinct. A similar condition was described by Ameuille (16) as a type of war nephritis to illustrate the rôle of infection as an aetiological factor in the production of this condition. We have included these cases in the present study in order that they might be distinguished from the typical cases of war nephritis.

From the beginning of this investigation, it seemed clear that although the majority of cases of war nephritis, even with marked initial symptoms, rapidly improved when put to bed and given a limited diet, yet others failed to respond to any of the usual methods of therapy. These two groups can be distinguished clinically and functionally. Whether the second or non-resolving group is a sequel of the first or only a more severe manifestation of the disease from the onset is difficult to determine. One fact is clear, however, that the non-resolving cases have a greater tendency to pass into a condition simulating chronic parenchymatous nephritis. The main distinguishing features of the two groups may be summarized as follows:

Resolving type. These cases arrived at the base relatively soon after the

onset of illness and were detained there a shorter time than the non-resolving type. During their stay very marked improvement occurred in their condition, a well-marked diuresis took place early in the disease, and was accompanied by the disappearance of headache, dyspnoea, &c. The blood-pressure fell rapidly. Retinal changes were infrequent, slight, and transient. Gross haematuria was rare and did not persist. Albumin and cylindruria decreased rapidly, and the specific gravity of the urine tended to rise to its normal level. All showed a good phthalein excretion, and the initial rise in blood-urea content quickly fell and remained low. Ambard's coefficient on evacuation was frequently normal. Chloride elimination by the urine was good. Acidosis tended to be slight, and the acid-base relationship was restored without alkali therapy.

Non-resolving type. Cases belonging to this group arrived at the base later in the disease and were detained there longer. Onset of diuresis was delayed, oedema tended to remain stationary or even to increase, marked secondary anaemia developed, and exacerbations of the disease were of common occurrence. Retinal changes were more frequent and permanent in character. Gross haematuria was a marked and persistent feature. Albumin and cylindruria did not clear up, and the specific gravity of the urine tended to remain low.

Phthalein excretion was diminished; the initial blood-urea content was higher, its fall much slower, and its subsequent course uncertain. On evacuation none of those examined showed a normal Ambard's coefficient. Elimination of chlorides in the urine was often poor and concentration low. Acidosis was more marked and persistent and alkali therapy was required to restore the acid-base balance.

Acute infective nephritis. This type of acute nephritis always followed a focus of infection already established in the body. Onset occurred with marked fever. Dyspnoea was absent and oedema was limited to slight swelling of the face. Gross blood was always present in the urine, but albumin was moderate in amount and quickly fell to a mere trace. The blood-pressure was low and never rose above 120 mm. Hg. There was no diuresis or marked polyuria during the stage of improvement.

Phthalein excretion remained relatively high, but there was a very marked urea retention and an elevated Ambard's coefficient. The urea figure in the blood quickly fell to the normal level and remained low, and on evacuation Ambard's coefficient in the one case examined was normal. Acidosis was present, but mild in degree.

In one of the severe relapses (W., Table III) already described, where the relapse was due to a staphylococcal epididymitis, the symptoms were comparable to an acute infective process. Fever was high and prolonged; phthalein excretion did not fall to a marked degree; the urea in the blood quickly fell, and on departure from hospital Ambard's coefficient was only slightly above normal. Thus here we had a condition of acute infective nephritis grafted on to a typical case of war nephritis.

Certain phenomena occurring in this disease are of great importance from an etiological and therapeutic standpoint. These will now be discussed in relation to our functional and pathological results.

Dyspnoea. Dyspnoea has been recognized as a common and distressing feature in war nephritis. A history of its presence at onset was given by all our cases, while on admission 75 per cent. of the patients still complained of respiratory distress. Bronchitis, pleural effusion, and congestion of the lung bases were undoubtedly often causative factors, yet certain cases had dyspnoea without pulmonary signs that could be distinguished clinically. This latter group suggested the possibility that the condition might be due to an altered acid-base relationship in the circulating blood. Although an acidosis was demonstrated in a majority of the dyspnoeic patients the condition was never as severe as that encountered in terminal chronic nephritis. With regard to the relationship between dyspnoea and acidosis in those cases free from clinical signs in the chest, three groups could be distinguished: First, dyspnoea associated with an acidosis sufficient to cause respiratory symptoms; this occurred in two fatal cases and two with recovery. Second, cases with dyspnoea and a slight or moderate degree of acidosis, which was not severe enough to give rise to respiratory symptoms. Third, cases without dyspnoea but showing a moderate acidosis. The natural conclusion from such evidence is that the degree of acidosis existing in the majority of these cases is not the main etiological factor in the production of dyspnoea.

Haematuria. Every case examined showed the presence of blood in the urine. This might on the one hand be microscopic in amount, or on the other might colour the urine a deep red tint. All gradations between these two extremes were present. This haematuria was often persistent, intractable to treatment, and showed a marked tendency to recur. The coagulation time of the blood in these cases when tested by Wright's method (17) was not delayed. The exhibition of calcium salts did not affect the bleeding. Many cases of war nephritis showed marked pathological changes in their blood-vessels. Three of our cases developed phlebitis. Another case had subcorneal haemorrhages. In the non-resolving group retinal haemorrhages were not infrequent. Post mortem, haemorrhagic areas were found in the endocardium, in the stomach and caecum, and in the spleen. None of our cases showed any miliary cerebral haemorrhages. Histologically the earliest change in the kidneys was found in the delicate vessels of the glomerular tuft and intratubular haemorrhage was marked in all stages.

After the injection of phenolsulphonephthalein gross blood was noted several times in the urine. That the colour was not due to the residue of phthalein in an alkaline urine was proved by counting the corpuscles in a specimen before and after the employment of this dye. In cases characterized by a hypersensitive kidney which tends to bleed at the slightest provocation this test is contra-indicated. In the great majority of cases its use produces no ill effects. This tendency to bleed after the employment of substances foreign to the organism for

diagnostic purposes has already been described in regard to indigo carmine by Trémolières and Caussade (18), and in regard to lactose by Trevan (19).

Oedema. The fact that a patient found himself unable to put on his boots some morning, or that a comrade noticed his feet swollen, was often the cause of his reporting sick to the medical officer. The most frequent seat of oedema was in the face, especially around the eyes, and over the sacrum and lumbar region. Oedema was also often present over the shins and around the ankle and instep. Oedema was sometimes more marked on one side than on the other. Small accumulations of fluid at the base of the pleural cavities were common, yet ascites, penile and scrotal oedema were only found in severe cases of the non-resolving type. Oedema might pass off quickly in a few days or might persist for three months or more. Disappearance was accompanied by a diuresis and a greatly increased excretion of chlorides. It was apt to recur when the patient was allowed to get up and move about.

The onset of oedema is so sudden that it is difficult to imagine that renal retention of water and chlorides is its primary cause. Oedema did not re-appear to any marked extent in those severe relapses where chloride retention was a marked feature. Again, in one of the relapsing cases (C., Table III), a marked chloride and water retention was accompanied by a fall of chloride concentration in the plasma well below the normal threshold. This, with a corresponding fall in haemoglobin, pointed to a condition of hydraemia yet without marked oedema. The degree of acidosis found as early as the fifth day in the case of K. A. (Table I) might suggest that acidaemia was the causative factor of oedema. The findings in certain cases, however, tend to negative such a conclusion. In two cases, although severe oedema was present, yet both had a normal acid-base relationship. Again, in Case W. (Table III), during relapse, the recurrence of acidosis was unaccompanied by any reappearance of oedema. In several cases of the non-resolving group the exhibition of alkali therapy, although quickly counteracting the existing acidosis, yet had no appreciable effect on the oedema. In addition, from other evidence, as is shown later, we have come to the conclusion that the acidosis found in acute nephritis is but a secondary phenomenon. Definite pathological evidence has been obtained of toxic action on the blood-vessels. This toxic feature also supplies a reasonable explanation of the onset of oedema, which is doubtless later aggravated by the retention of water, salt, and waste metabolic substances within the organism.

Diuresis. Spontaneous diuresis was often the first and surest sign of convalescence. Preceded usually by oliguria, the diuresis soon resulted in the excretion of fluid and other retained substances. A definite and well-marked diuresis occurred in 66 per cent. of this series of cases, and much earlier in the resolving than in the non-resolving type. The urinary findings resembled closely the chloride diuresis produced experimentally in animals, though retained substances other than water and chlorides as urea were often excreted. Onset of diuresis might occur early in the course of the disease or be delayed even for weeks. No definite clinical or functional cause was observed

for this sudden increase in urinary output. If a definite causative factor for the onset of diuresis could be determined, or a therapeutic agent discovered for its inception, the treatment of many difficult and tedious cases would be simplified. If no relapse follows the diuresis, a good immediate prognosis can be expected.

Convulsions. Convulsive seizures occurred in six cases in this series. Three of these ultimately died; of the remainder, two belonged to the resolving and one to the non-resolving group.

The onset of convulsions as a rule took place early in the disease. Only in one case (J. B., Table IV) did convulsions occur later than the eighteenth day of illness, and in this case took place on the thirty-ninth day, six days before death. In two of the cases there were well-marked premonitory symptoms taking the form of a feeling of numbness and loss of power in the arms. Accompanying this in one case (E. B., Table I), an educated and intelligent man, was a presentiment of impending evil. Two hours later a convulsion occurred. Seizures were of all grades of severity, from twitchings of localized groups of muscles to typical epileptiform fits. In one fatal case these fits were recurrent and severe; in another case (J. N., Table I), who subsequently made a good recovery, six violent convulsions occurred within three hours. The fits in some patients were followed by a condition of hebetude, in others by wild delirium. The persistence of the comatose condition was of bad prognostic significance. Patients making a good recovery woke up after a heavy sleep, with headache perhaps, but with a clear mind and no recollection of what had occurred. Often the contrast between the sane man and the maniac of the day before was most striking. The case E. B. (Table I), whose fit was preceded by a definite aura, noticed that for two days afterwards he had not regained full power in his arms, that he wrote with difficulty, and that his writing was unsteady. The blood-pressure some time after the convulsions was high, as a rule about 180 mm. Hg. In the case E. B., during the prodromal stage the blood-pressure was 150 mm. Hg, but some hours after the fit had risen to 180 mm. Hg. A similar observation is noted by Abercrombie (20). In one case (J. B., Table IV) the blood-pressure taken immediately after convulsion had subsided was only 150 mm. Hg.

In two cases at the time of convulsions, the blood-urea was normal in one case (E. B., Table I) and only slightly raised in the second (J. N., Table I). As a matter of fact E. B. had almost normal renal function at this period. In three cases, as shown by the alveolar CO_2 tension and combined CO_2 of the blood, there was a mild acidosis, but that this was not a causative factor is shown by a fatal case on alkali therapy, whose alveolar CO_2 was 43 mm. Hg and combined CO_2 of blood as high as 90 c.c. In two cases whose cerebro-spinal fluid was examined the hydrogen ion concentration of this fluid was not raised.

Owing to the similarity of these convulsions to those seen in eclampsia, the lipase content of the blood was examined with a view to possible liver involvement (21). In all cases examined, however, the lipase content was normal.

Convulsions are thus seen in every type of war nephritis, in those that terminate fatally and in those that make a good recovery; in resolving and in

non-resolving; in those whose renal secretion is good, and in those in whom it is practically in abeyance; in cases showing a mild acidosis and in those saturated with alkali. The occurrence of convulsions is not necessarily of bad prognostic import.

Relapses. Relapses were of frequent occurrence and no type of case was immune. Intercurrent affections, to which these patients were very susceptible, always seemed to precipitate a relapse of varying severity. In some instances no cause could be discovered; that some of these idiopathic relapses occurred towards the end of a copious diuresis is suggestive.

Clinically a relapse was marked by a rise of temperature, by the appearance of gross blood in the urine, and by a fall of blood-pressure. Recurrence of oedema was slight enough to be easily overlooked. Dyspnoea did not recur at all. The functional disturbances attendant on a relapse were much more severe than the clinical symptoms would suggest. There was a marked fall in the excretion of water and of urea, in the chloride concentration of the urine, and in the excretion of phthalein. The total non-protein nitrogen rose to a high level in the blood and contained a higher percentage of urea than before. With restoration of water output the excretion of urea quickly improved and the blood-urea fell, although Ambard's coefficient remained elevated; but the kidney only very slowly recovered the ability to excrete chlorides and phthalein.

The acid-base relationship in the blood. The alveolar CO_2 tension was determined in 80 per cent. of the cases shortly after admission. No alkali therapy had been previously given. With a single exception the readings obtained varied between 25 and 35 mm. Hg. These findings indicated an early mild acidosis, and this assumption was confirmed in half the cases by simultaneous estimations of the alkali reserve of the blood-plasma. The methods employed for demonstrating an acidosis, though based on different experimental principles, gave for practical purposes parallel results. In cases that recovered, the acidosis, though definite, was never marked. The lowest values were: alveolar CO_2 tension 23 mm. Hg, RpH 7·8, combined CO_2 37 c.c. In one fatal non-resolving case the alveolar CO_2 tension progressively decreased, reaching the low figure of 15 mm. Hg before death. The acidosis was usually less marked in the resolving type, and as a rule disappeared without the use of alkali therapy. When alkali was administered by mouth the urine soon became alkaline and the plasma reserve normal. The fact that in the non-resolving type more alkali was required to maintain the normal acid-base balance in the body pointed to more severe acidosis. Thus the degree of acidosis would appear to be definitely related to the extent and duration of the kidney lesion. This fact, taken with other evidence, shows how closely the acidosis is associated with impaired renal function. The acidosis was always accompanied by retention of substances normally excreted by the kidney, and spontaneous recovery from the acidosis followed the rapid elimination of these substances. We have also demonstrated that an acidosis may occur on two different occasions in the same patient (W., Table III). In this instance there was a deficiency of the reserve alkalinity

during the first week, a quick recovery to the normal, but with relapse later a return of the acidosis. These facts indicate that the degree of acidosis met with in cases of war nephritis is secondary to impaired renal excretion. More direct evidence of a deficient acid elimination by the kidney has recently been brought forward by Marriott and Howland (22), who showed that the inorganic phosphates of the blood were increased in certain cases of chronic nephritis in which acidosis is present. We are now investigating the relationship of the inorganic phosphates of blood and urine in cases of war nephritis, in order to ascertain whether their retention is the important factor in producing the acidosis.

Functional tests. Functional tests must be undertaken in cases of war nephritis in order to secure the best method of treatment and to form a prognostic opinion of any real value. Had we depended solely on clinical observation the gravity of certain cases would have been entirely overlooked.

The phthalein test gave very valuable information and gave it very quickly. Failure to excrete the dye or to excrete it in more than a mere trace was, with the exception of two very severe relapses, seen only in cases which ultimately proved fatal. Values below 25 per cent. were evidence of a very badly damaged kidney and warranted a very guarded prognosis. An excretion between 25 per cent. and 40 per cent. was characteristic of the non-resolving group and was an indication that progress would be tedious. A reading above 40 per cent. was found in all the resolving cases on admission with one exception (J. N., Table I). From a reading above 40 per cent., however, one cannot definitely state that the functional powers of the kidney are good. We have found cases with a phthalein excretion above this which, nevertheless, had a very definite renal impairment, and even one fatal case which had a phthalein excretion of 50 per cent. four days before death. On the other hand, J. N. (Table I), who had a phthalein excretion of only 25 per cent. just after a series of convulsions, rose a week later to 60 per cent. and showed the marked clinical improvement typical of the resolving group. Widal and his collaborators (23) have shown that in chronic nephritis the excretion of phthalein gave results parallel to Ambard's coefficient. The work of Rowntree and Marshall, Boyd (24), and Lewis (25) has shown that this is not strictly true in all cases of chronic nephritis. Our results demonstrate that in acute nephritis there is no absolute parallelism between the two. In the early stages of the disease a good phthalein excretion coexisted with a retention of urea and a high Ambard's coefficient. For instance, A. H. (Table II) showed on the fifth day of illness a phthalein excretion of 45 per cent., a blood-urea of 77 mg. per 100 c.c., and an Ambard's coefficient of 0·148, and other instances can be found on reference to the tables. On the other hand, in two of our cases of severe relapse the phthalein excretion was cut off at once to a mere trace before the urea retention had time to develop; with a return towards normal function the blood-urea content dropped to a normal level, while phthalein was only 33 per cent. This result agrees closely with the findings of Lewis and Rivers (26) in a case of bichloride poisoning. In cases progressing

satisfactorily the blood-urea content dropped rapidly, while the excretion of phthalein did not show a corresponding rise. As a rule a high phthalein excretion in the early stages of the disease, even although accompanied by a high urea figure in the blood, was a good prognostic feature.

The estimation of the amount of urea in the blood was of great value, if, in a patient on a known diet, the figure was raised. This gave definite information as to impaired function. A normal figure, however, did not rule out kidney involvement, and it was in this type of case, often accompanied by a good phthalein excretion, that the estimation of Ambard's coefficient was of great service. As an example of this the following case may be cited. H. W. (Table II), one of the non-resolving group, had a phthalein excretion of 50 per cent., blood-urea content of 43 mg. per 100 c.c., and an Ambard's coefficient of 0·134. His oedema had almost cleared up. A week later oedema was absent, phthalein excretion was 46 per cent., blood-urea content 54 mg., and Ambard's index stood at 0·156. The slight fall in phthalein excretion and rise in blood-urea content would not have attracted much attention, as his clinical condition appeared to be improved, had not his Ambard's coefficient been markedly raised, which aroused the suspicion that despite apparent clinical improvement progressive renal impairment was taking place. This was corroborated by further functional studies a week later, as phthalein excretion had now fallen to 40 per cent., blood-urea content had risen to 60 mg., and Ambard's coefficient to 0·165.

The estimation of the chlorides in the urine was of the greatest value in differentiating the groups. On arrival at the base the resolving group were all passing a urine of normal or raised chloride concentration. In the non-resolving group, however, the chloride concentration was very low in half the cases. It would be interesting to know if the concentration was lowered in every case at the beginning of the illness. Judging from the large total amount of salt passed during the period of diuresis, chloride retention must have been of some duration. In the relapsing cases, both in mild and severe forms, the sudden fall in chloride concentration was the most prompt warning of the recrudescence of the malady. The primary rise in chloride concentration in certain of these cases just before the marked fall is noteworthy. The explanation of this finding opens up many fascinating theories which will at once suggest themselves to the reader. As a rule a low phthalein excretion accompanied a low chloride concentration. In the relapsing cases phthalein and chloride excretion closely simulated one another, both in their quick cessation and in their slow return to normal. This contrasted with the urea concentration in the urine, which did not fall relatively as low as the chloride, and with the onset of diuresis rose quickly to its original level, as if flushed out of the system with the re-establishment of water output. In two of our fatal cases (R. B. and F. G., Table IV), however, which showed a mere trace of phthalein excretion, the urine contained a relatively high chloride concentration until death, although, owing to the small output of urine, the total excretion was very small. In these cases

the chloride concentration of the plasma was above the threshold. In the cases of acute infective nephritis we find a relatively good phthalein excretion, accompanied by a low chloride concentration in the urine, though the plasma concentration was above the threshold; a similar condition existed in the relapse (W., Table III) due to definite microbic condition. Although in one case, W. V. (Table II), and in two fatal cases, S. J. and J. B. (Table IV), a low chloride concentration accompanied a plasma chloride concentration below the threshold, yet in many other cases inability to excrete chlorides was associated with a plasma concentration well above the threshold level. Chloride concentration is a very complex problem, and may depend on many factors not yet clearly understood, nevertheless the chloride concentration of the urine remains a very sensitive index of kidney function. A continued low chloride concentration in the urine is of unfavourable prognostic significance.

It is difficult to evaluate the results given by the addition of salt to the diet. As a rule, those cases which have been shown by other functional tests to have impaired renal function excrete the extra salt badly, responding neither by a markedly increased output of water nor by a raised chloride concentration. On the other hand, the case which showed the lowest Ambard's coefficient (0·071) in the resolving group gave the worst response to this test. On the whole, however, cases with good renal function excrete the additional salt satisfactorily.

These results show that it is not safe to dogmatize from one type of renal functional test alone; but a combination of the tests described above is of the utmost value in forecasting the immediate course of the disease. Time alone will demonstrate their value in ultimate prognosis.

Summary.

1. Cases of war nephritis can be divided into two groups:
   Resolving and non-resolving.
2. The resolving group is characterized by:
   (*a*) Rapid disappearance of oedema accompanied by a distinct diuresis, copious excretion of chlorides, and fall in blood-pressure.
   (*b*) Rapid diminution in amount of albumin in urine.
   (*c*) Relatively good renal function.
3. The non-resolving group is characterized by:
   (*a*) Slow disappearance of oedema and delayed diuresis.
   (*b*) Persistent gross haematuria and persistence of albumin in the urine.
   (*c*) Development of permanent retinal changes.
   (*d*) Grave impairment of renal function.
4. The acute nephritis following a focus of infection is a distinct entity from war nephritis.
5. Relapses are of frequent occurrence in both types of the disease and are

of serious prognostic significance. Functional studies during relapse give many interesting results as regards the different methods of excretion of different substances by the kidney.

6. An acidosis of moderate degree is present. In the resolving group this disappears with general improvement, but in the non-resolving group alkali therapy is required to restore the normal acid-base relationship.

7. Functional tests are of the greatest value in forming an opinion as to the extent of renal impairment. The gravity of certain cases may be entirely overlooked if one depends on clinical observation alone. In the early stages of the disease the excretion of phenolsulphonephthalein, the urea content of the blood, and the concentration of the chlorides in the urine are the most helpful. When the acute symptoms subside and the above tests give more or less normal results, Ambard's coefficient often shows evidence of a damaged kidney.

8. Prognosis as to ultimate complete recovery, even in the resolving group, must be guarded. In the non-resolving group many cases show relatively early in the disease evidence of permanent renal change.

9. The exhibition of alkali therapy is of distinct service in many cases, as shown not only by a restoration of the normal acid-base relationship in the blood, but also by an improvement in renal function.

10. In cases dying in the first two weeks of the disease an intracapillary glomerulitis is the most striking histological feature; in cases in which death has occurred in the fifth week there is found, in addition, a proliferation of the cells lining Bowman's capsule, intense oedema of the interstitial tissue, small round-celled infiltration and flattening of the epithelium lining the convoluted tubules. Cases in which death has been delayed to the seventh week of the disease show the proliferated cells of Bowman's capsule replaced by fibrous tissue, with resulting sclerosis of the Malpighian tuft, increase of interstitial tissue, and widespread and severe tubular changes.

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TABLE I.

Patient. Age. Date of Admission.	Day of Disease.	Temp.	Oedema.	Blood Pressure. mm. Hg.	Urine. Amount in c.c.	Sp. Gr.	Alb. %	Gross Blood.	Chloride %
J. S., 28, 10/iv/17	6	99	+ +	150	1320	1·020	0·4		0·18
	16	N	0	105	4300	1·008	0·02		0·30
	41	N	0	105	2420	1·014	0·17		0·27
A. B., 31, 14/iv/17	10	N	+ + +	120	1065	1·014	0·25		0·17
	14	N	+ +	110	1635	1·010	0·08		0·24
	31	N	0		1560	1·008	0·05		0 21
	41	N	0	115	1195	1·016	0·07		0·39
K. A., 20, 23/iv/17	5	99	+ + +	160	2425	1·010	0·10		0·39
	12	N	0	100	1635	1·012	0·05		0·30
	28	N	0	100	1575	1·017	0·05		0·32
L. E., 36, 9/v/17	10	N	+ +	145	1965	1·010	0·18		0·30
	26	N	0	120	2145	1·010	0·04		0·38
	37	N	0	120	1820	1·010	0·05		0·27
J. B., 37, 28/v/17	11	100·4	+ +	170	1225	1·014	0·10		0·33
	32	N	0	105	915	1·015	0·04	+	0·39
F. G., 28, 30/v/17	6	N	+	140	2600	1·010	0·30		0·43
	29	N	0	115	2125	1·015	0·15		0·31
L. S., 21, 7/vi/17	13	99	+ +	150	1445	1·010	0·25		0·39
	31	99·8	0	140	2240	1·007	0·12		0·29
	49	N	0	100	1100	1·014	0·08	+	0·38
B. W., 22, 21/vi/17	9	100·8	+ +	145	1226	1·012	0·10		0·68
	16	N	0	108	2425	1·006	0·03		0·44
	23	N	0		755	1·020	0·08		0·57
	38	N	0	115	1050	1·014	0·03		0·43
W. T., 19, 28/vi/17	6	100	+	165	805	1·012	0·10		0·65
	10	N	0	120	1150	1·008	0·04		0·26
	38	N	0	115	1200	1·012	0·20		0·33
	53	N	0	135	1440	1·013	0·08		0·38
J. N., 42, 9/vii/17	14	N	+ +	160	1150	1·006	0·10		0·27
	22	N	0	120	1500	1·006	0·06		0·40
	38	N	0	115	2025	1·009	0·12		0·36
E. I., 41, 30/viii/17	7	N	+ +	120	2215	1·007	0·01		0·54
	16	N	+	105	2300	1·005	0·01		0·30
	19	N	0	125	2090	1·005	0·01		0·37
	39	N	0	105	1615	1·014	0·01	+	0·35
E. B., 40, 14/xi/17	9	99	+ + +	130	1800	1·012	0·10		
	13	99	+ + +	185	1920	1·009	0·06		0·60
	23	N	0	110	2030	1·008	0·03		0·45
	36	N	0	110	1150	1·017	0·03		0·40

Resolving Group.

Phthalein.	Blood.			Ambard's Coefficient.	Acid-base Relationship.			Remarks.
%	Chloride mg. per 100 c.c. Plasma.	Urea mg. per 100 c.c.	T.N.P.N. mg. per 100 c.c.		Alv. CO_2 Tension. mm. Hg.	RpH.	Combined CO_2 of Plasma volume %.	
65	685		62					
	613		32					
69	598							
55	654		50					
	597							
62	648		39		33	8·1		
60	631				37	8·2		
62	658		47		25	7·9		
	570		43					
75	606		29		38			
60	666		53		33	8·0		Previous attack of war nephritis, June, 1915; in hospital till Nov., 1915; returned to France, Jan., 1917
	580		33					
66	553	31	27		39			
66	612	46	41		30			
50	636	32	38	0·71	38			
62	621	32	30		35			
62	608	32	29	0·077				
61	582	41	34		35			
62	565	44	38					
62	600	40			37			
51	630	40		0·086	35			
	586	33						
50					40			
51	646	57	41		32		40	
	627	60			35		50	
40	648	46			40		51	Sodium bicarbonate, 16 grm. per diem from 40th day of disease
55	611	32	34		44	8·35	63	
25	650	49	42		35	8·2	48	Convulsions on admission
60	612	37		0·121	37	8·3	58	
57	627	40			40		54	
50	625	47			40		57	
52	591	38						
	633	35			40			
62	600	26			43		65	
60		40	37	0·091	33		46	Convulsion on 12th day of disease
71		31	37	0·090	42		58	
71		39	43	0·080	40		58	

Patient. Age. Date of Admission.	Day of Disease.	Temp.	Oedema.	Blood Pressure. mm. Hg.	Urine. Amount in c.c.	Sp. Gr.	Alb. %.	Gross Blood.	Chloride %.
W. C., 38, 7/iv/17	10	N	+ +	106	850	1·010	0·50		0·06
	31	N	+	95	2340	1·010	0·38	+	
	55	99°	Tr.	140	2735	1·010	0·25		0·20
	76	N	0	110	2160	1·010	0·15	+	0·20
	82	N	0	110	2450	1·009	0·10	+	0·29
A. S., 39, 11/iv/17	14	N	+ + +	120	1605	1·010	0·70		0·05
	36	99°	+		1800	1·010	1·00		0·27
	57	N	0	115	2140	1·014	0·70		0·43
H. S., 38, 1/v/17	8	N	+ +	145	1370	1·012	0·20		
	30	N	+ +	138	1500	1·010	0·15		0·34
	50	N	0	120	2610	1·008	0·04		0·28
	58	N	0	125	1500	1·010	0·04	+	0·33
J. K., 25, 2/v/17	17	N	+ + +	120	1805	1·010	0·45		
	27	99°	+ +	135	1800	1·014	1·10		0·16
	51	N	0	122	1440	1·010	0·23	+	0·08
	92	N	0	130	2400	1·005	0·12	+	0·29
	99	N	0	140	2160	1·009	0·60	+	0·29
S. H., 19, 30/v/17	6	99°	+ + +	130	1760	1·020	0·10		0·37
	30	N	Tr.	110	1785	1·010	0·10	+	0·31
	42	N	0	104	1410	1·007	0·05		0·21
	61	N	0	105	1825	1·010	0·04		0·33
	69	100°	0	90	1600	1·010	0·10	+	0·19
	83	N	0	115	1800	1·008	0·03		0·26
J. T., 42, 4/vii/17	6	99°	+ + +	170	440	1·022	0·80		0·43
	16	N	+ +	108	1260	1·015	0·80		0·44
	40	N	Tr.	130	1850	1·005	0·30	+	0·43
	53	99°	0	120	1985	1·007	0·30	+	0·36
A. H., 35, 21/vii/17	5	N	+ + +	165	1340	1·009	0·70	+	0·27
	16	N	+ + +	140	1540	1·019	0·44		0·63
	49	100°	0	105	2115	1·013	0·01	+	
	56	N	0	120	2210	1·013	0·01		0·17
W. V., 48, 7/viii/17	13	N	+ +	165	606	1·009	0·70		0·09
	20	N	+ + +	165	865	1·011	1·20	+	0·06
	28	99°	+ + + +	160	1015	1·013	1·60	+	0·03
	37	N	+ + + +		1170	1·010	1·00	+	0·02
	71	N	+ +	170	1780	1·008	0·70		0·21
	93	99°	+	170	2382	1·013	0·55	+	0·38
W. G., 46, 23/viii/17	9	N	+ + +	140	495	1·012	0·40		0·13
	21	99°	+ + +	120	1320	1·018	0·10		0·12
	50	N	0	135	2570	1·006	0·10		0·33
	67	N	0	115	2300	1·014	0·08		0·42
H. W., 39, 12/x/17	18	N	+ + +	170	680	1·027	0·40		0·30
	25	N	+ +	140	1990	1·008	0·40		0·33
	44	N	+	130	2100	1·011	0·20	+	0·50
	58	N	0	110	2210	1·008	0 12		0·39
	65	N	0		1460	1·014	0·18		0·40

Phthalein.	Blood.			Ambard's Coefficient.	Acid-base Relationship.			Remarks.
%	Chloride mg. per 100 c.c. Plasma.	Urea mg. per 100 c.c.	T.N.P.N. mg. per 100 c.c.		Alv. CO_2 Tension. mm. Hg.	RpH.	Combined CO_2 of Plasma volume %	
20	613		65					
	672		56		23	7·8		
29	590		37		39	8·2		Sodium bicarbonate, 16 grm. per diem, 41st–63rd day of disease
21	640	132	73	0·333	30		37	Sodium bicarbonate, 16 grm. discontinued, 63rd–76th day of disease
18	656	158			35		54	Sodium bicarbonate, 16 grm. readministered, 77th–82nd day of disease
38	645		87		25			
60	650		30		25	8·1		Sodium lactate, 16 grm. per diem, 39th–57th day of disease
64	600	41	37		35			
50	619		32		28	8·1		
40	565		29		35			Sodium bicarbonate, 25th–50th day of disease
36	596	28	32					
44	633	44	37		38			
	653		48		25	7·8		Sodium lactate, 17th–73rd day of disease
					38	8·2		Sodium lactate discontinued, 73rd day of disease
48	562	46	40					
44	660	88	64	0·175	28	8·1	39	Sodium bicarbonate, 92nd–99th day of disease
	639	37			40	8·3	73	
43	665	63	59		35			
33	598	60	44	0·147	35			
	604	83						
31	662	52		0·131	35		43	
	641	87				8·2	48	Sodium bicarbonate, 70th–83rd day of disease. Relapse following tonsillitis
42	583	36	37		42	8·3	66	
55	632	43			33	8·1	46	
	666	35			30		53	
55	626	26			40	8·4	57	
50	557	40			40			
45	642	77		0·148	28	8·2	47	Sodium bicarbonate, 13th–56th day of disease
	638	33			40	8·4		
57	607	52			43			
52	593	45			42			
17	624	137						Sodium bicarbonate, 13th–93rd day of disease
	552	140	94					
10	511	113	84		42		55	
	490	102	68		42	8·4	82	
31	600	51	46		42		73	
22	601	52	40	0·161	43		67	
32	658	140	103		28	7·9	37	
50	594	71			39		59	Sodium bicarbonate, 14th–67th day of disease
42	622	31		0·101	43		59	
62	587	35	30	0·098	45			
48		90	74		32		43	Convulsion on admission
59		32	27	0·100	40		54	
50		43	37	0·134	40		54	
46		54	42	0·156	40		50	
40		60	48	0·165	38		47	

TABLE III.

Patient.		Temp.	Oedema.	Blood Pressure.	Urine.				
Age. Date of Admission.	Day of Disease.				Amount in c.c.	Sp. Gr.	Alb. %	Gross Blood.	Chloride %.
B., 36, 10/iv/17	6	N	++	175	2770	1·010	0·04		0·29
	11	102·4°	0	145	2450	1·010	0·05	+	0·42
	13	100·4°	0	115	1300	1·010	0·10	+	0·17
	15	N	0		750	1·010	0·09	+	0·13
	20	N	0	120	1120	1·012	0·07		0·21
	38	100·4°	0	135	2505	1·010	0·05	+	0·21
	51	N	0	140	1715	1·008	0·05		0·30
	62	101°	0	125	1700	1·010	0·05	+	0·34
C., 34, 12/v/17	6	N	++	130	585	1·012	0·70		0·47
	13	N	0		2820	1·010	0·30		0·32
	23	101°	0		1255	1·020	0·40	+	0·64
	24	98·8°	0	106	600	1·014		+	0·14
	25	N	Tr.	105	280	1·011	0·40	+	0·14
	30	N	Tr.	140	210	1·012	0·05	+	
	35	N	Tr.	126	775	1·013	0·10	+	0·09
	39	N	Tr.	132	2610	1·006	0·06	+	0·09
	45	99°	Tr.	135	2995	1·006	0·04	+	0·14
	50	100°	Tr.	145	2650	1·009	0·12	+	0·17
	57	N	Tr.		2320	1·007	0·10	+	0·20
	65	N	0	160	2390	1·005	0·08		0·19
	85	N	0	136	1575	1·009	0·10		0·26
	89	N	0	160	2320	1·010	0·10		0·34
E., 34, 17/v/17	9	N	+++	150	1805	1·014	0·27		0·58
	15	N	0	140	2885	1·008	0·10		0·54
	19	100°	0		1295	1·010	0·42	+	0·29
	20	98·6°	0		1925	1·008	0·20	+	0·12
	22	99°	0	110	1050	1·010	0·10	+	0·20
	26	N	0	130	1990	1·008	0·10	+	0·07
	34	N	0	122	1610	1·008	0·12	+	0·15
	41	N	0	120	1720	1·010	0·08	+	0·06
	53	N	0		2035	1·004	0·12		0·13
	64	N	0	108	2200	1·005	0·05		0·20
W., 27, 9/viii/17	4	N	+++	135	415	1·018	0·40		0·25
	13	99°	Tr.	120	2720	1·005	0·10		0·27
	20	99·6°	0	125	1260	1·020	0·50		0·62
	21	103·4°	0		1820	1·015	0·70		0·94
	22	100·8°	0	130	930	1·030	0·50	+	0·25
	23	101·4°	0		740	1·025	1·60	+	0·01
	30	100·8°	0	115	1920	1·005	0·10	+	0·04
	39	99·6°	0	95	2185	1·006	0·20	+	0·07
	48	100°	0	95	2180	1·005	0·60	+	0·12
	57	99·4°	0	100	1985	1·005	0·30	+	0·25
	64	99·4°	0	105	2070	1·005	0·30		0·34

Relapses.

Phthalein.	Blood.			Ambard's Coefficient.	Acid-base Relationship.			Remarks.
%	Chloride mg. per 100 c.c. Plasma.	Urea mg. per 100 c.c.	T.N.P.N. mg. per 100 c.c.		Alv. CO_2 Tension. mm. Hg.	RpH.	Combined CO_2 of Plasma volume %.	
61	637		25					
								Onset of relapse
Tr.	640		117		28	7·9		Sodium bicarbonate, 16 grm. per diem from 21st day of disease
20	600				40			Trace of oedema on the 27th day of disease
35	566		44					
42	561	33	32					
36	631		44			8·1		
62					38			
								Onset of relapse with severe pains in shins and ankles
					36			On sodium bicarbonate from commencement of relapse
Tr.	564	90	66		39	8·4		
	418	215	133					
	468	220	142		40			
Tr.	516	204	135	0·610				
	612	130	83		40			
5	550	111	70	0·303	42		67	
	582	95	57					
19	605	60	47	0·162				
	602	46	38		42	8·4	61	
33		44		0·116	42			
63	628		48		30	8·2		
66								
								Onset of relapse
20	600	50	39					Rigor on 21st day of disease. Herpes labialis. Temp. 101·8°. Put on sodium bicarbonate.
					35			
								Phlebitis on 28th day of disease. Temp. 99°
14	561	93		0·266				
					38			
	560	62						
31	630	56	43	0·124				
50	681	70			30	8·15	45	
60	590	48			40	8·25	54	Pus marked in urine
	575	33			40		49	
								Epididymitis and onset of relapse
50	550	52			40		55	
33	559	110			33	7·9	39	
	578	138			35		46	
54	608	41			42		51	
60	617	35		0·0920	40		54	

TABLE IV.

Patient.		Temp.	Oedema.	Blood Pressure.	Urine.				
Age. Date of Admission.	Day of Disease.				Amount in c.c.	Sp. Gr.	Alb. %	Gross Blood.	Chloride %
P. R., 32, 3/xii/16	13	N	+ + +	190		1·020			
	14	103°	+ + +			1·020			
J. G., 24, 12/xii/16	8	N	+ + +	150	1000				
	9	100·4°	+ + +	145	1600				
	10	N	+ + +	170	2000				
	11	99°	+ + +		2200	1·022			
	12	100°	+ + +		1700				
	13		+ + +	180					
F. G., 26, 13/iii/17	21	99°	+ + +	170	800	1·020	1·10		
	25	N	+ + +	115	1070	1·014	1·00		
	28	N	+ + +		980	1·014	1·00		0·08
	34	N	+ + +	140	725	1·012	0·50		0·21
	46	N	+ + + +		100	1·012	0·50		0·26
	51	Sub. N	+ + + +	135	125	1·012	0·50		0·32
	52	Sub. N	+ + + +	100					
R. B., 33, 14/iii/17	24	101°	+ + +		2700	1·014	0·30	+	
	29	99°	+ + +	125	1050	1·010	0·20	+	
	32	N	+ + +	135	145	1·010	0·30	+	0·27
	33	99·4°	+ + +	145	128			+	
S. L., 25, 5/iv/17	7	N	+ +		300		1·20		
	12	N	+ +		300		1·20		
	16	N	+ + +		330	1·014	1·20		
	18	N	+ + +	145	275	1·020	0·80		0·01
	19	N	+ + + +		375	1·020	1·20		0·01
	26	N	+ + + +	130	50		0·70		
	32	N	+ + + +						
J. B., 22, 26/vi/17	32	100°	+ +	180	540	1·007	0·04	+	
	34	101°	+ +	155	520	1·008	0·04	+	0·09
	36	100°	+ + +	150	535	1·009	0·05	+	0·04
	39	101°	+ + + +	140	390	1·010	0·10	+	0·03
	42	100·6°	+ + + +	170	415	1·009	0·20	+	0·02
	44	100°	+ + + +	146	150			+	
C. M., 28, 9/x/17	7	103°	+ + +	180	670	1·017	1·60	+	
	14	102°	+ + +		1840	1·011	0·60	+	
	15	101·5°	+ + + +		460	1·012	1·10	+	0·08
	16	103°	+ + + +	135	570	1·014	0·60	+	0·14
	17		+ + + +	160					

Fatal Cases.

Phthalein.	Blood.			Ambard's Coefficient.	Acid-base Relationship.			Remarks.
%	Chloride mg. per 100 c.c. Plasma.	Urea mg. per 100 c.c.	T.N.P.N. mg. per 100 c.c.		Alv. CO_2 Tension. mm. Hg.	RpH.	Combined CO_2 of Plasma volume %	
					25			Convulsion, coma
10								Death
50								
								Repeated convulsions, delirium, and death
5	662							
	688							
	689				25			
					15			Epistaxis, severe pains in legs. Drowsy
	624		252		15			
								Died
								Phlebitis. Blood culture sterile
Tr.	662	446						
					25			Died on 34th day of disease
Tr.	556		196		20			
								Subcorneal haemorrhages
	495		202			7·8		Evacuated to England
								Muscular twitchings. No convulsions
								Died 34th day of disease
2	598	173	104		30		37	Sodium bicarbonate 16 grm. per diem, 32nd–45th day of disease
	528	202			35		53	
	508	183			42		77	
	476	177			42		77	Convulsion. Blood-pressure taken just after 155 mm. Hg
								Muscular twitchings
	440	199				8·35	90	Coma. Died 45th day of disease
		204						Prostatic abscess. Epididymitis. Blood culture: Staphylococcus aureus. Pericardial rub. Wassermann's reaction—negative
	566	240	160			8·0	32	
								Died

DESCRIPTION OF FIGURES.

PLATE 16, FIG. 1. Section of kidney from J. G., who died on 13th day of disease, showing two glomeruli exhibiting cellular proliferation. One glomerulus has protruded into the proximal convoluted tubule. × 80.

FIG. 2. Section of kidney from R. B., who died on 34th day of disease. The glomeruli are lobulated. Two show early proliferation of the cells lining Bowman's capsule, while in a third this has progressed farther and a large mass of cells partially fills the capsular space. The tubules are separated by young oedematous connective tissue. Some areas are infiltrated with small round cells. The epithelium of the tubules is flattened; some tubules contain casts, others blood or large mononuclear cells. × 60.

FIG. 3. Section of kidney from J. B., who died 45th day of disease. Note the crescentic thickening of Bowman's capsule; one glomerulus is almost obliterated. The tubules are dilated; some contain casts, hyaline and granular; others blood or large mononuclear cells. × 50.

FIG. 4. Higher power view (× 180) of a glomerulus seen in Fig. 2, showing lobulation of tuft, proliferation and desquamation of cells of Bowman's capsule, and surrounding small round-celled infiltration.

FIG. 5. Higher power view (× 180) of a glomerulus from same kidney as Fig. 3, showing strangulation of Malpighian tuft and obliteration of capsular space by newly-formed connective tissue which has largely replaced the proliferated cells of Bowman's capsule.

FIG. 6. Section of kidney from C. M., who died on 17th day of disease. In this case war nephritis was complicated by a staphylococcal septicaemia. This section shows exudation of blood and leucocytes into the capsular space. In one glomerulus the resulting fibrin formation partially fills up the capsular space and can be seen plugging the proximal convoluted tubule for a considerable distance. The majority of the tubules contain red blood corpuscles and the interstitial tissue is invaded by polymorphonuclear leucocytes. × 50.

PLATE 17, FIG. 7. High power drawing from a section of same kidney as Fig. 1, showing a portion of glomerulus with proliferation of endothelial cells in the glomerular capillaries. The nuclei of one of these cells shows mitotic division.

FIG. 8. High power drawing from a section of kidney of J. D., who died on the 31st day of disease. The glomeruli show multiplication of the nuclei lining Bowman's capsule. Just at the mouth of the proximal convoluted tubule of the central glomerulus a collection of proliferated cells is seen. The Malpighian tufts, still enlarged, show marked cellular proliferation and an absence of red blood corpuscles. Lobulation is not marked and there is no invasion by fibrous tissue. The interstitial tissue is very oedematous and contains areas of small, round-celled infiltration. The widely separated tubules are dilated, their epithelium is flattened; mitotic figures (marked A) are frequent, and their lumen often contains granular débris, mononuclear cells, and red blood corpuscles.

PLATE 18, FIG. 9. High power drawing from same section as Figs. 3 and 5, showing proliferation of cells of Bowman's capsule with formation of crescent and its invasion by fibrous tissue. Lobulation and fibrous thickening of Malpighian tuft. Connective tissue can be seen passing into adjoining interstitial substance of kidney, which is increased in amount. Some of the tubules are seen containing casts, hyaline or granular, with nuclear remains; others contain blood or large mononuclear cells. Tubular epithelium is swollen and irregular; sometimes flattened. In one tubule hyaline droplet formation is well seen.

We are indebted to Captain C. H. Hopwood for the micro-photographs, to Sergeant A. K. Maxwell, R.A.M.C., for the drawings, and to Mr. R. M. Steven, Queen's University, Belfast, and Sergeant W. J. Clayden, R.A.M.C., for preparation of the microscopic sections.

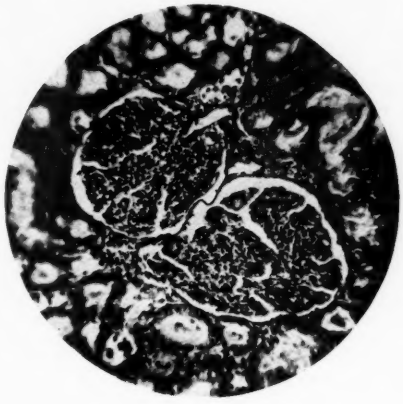


FIG. 1



FIG. 2

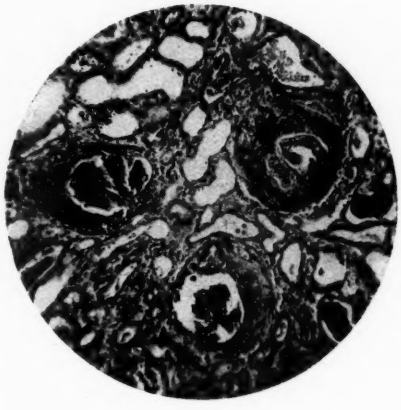


FIG. 3

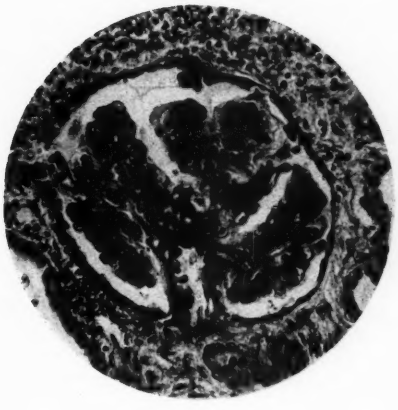


FIG. 4

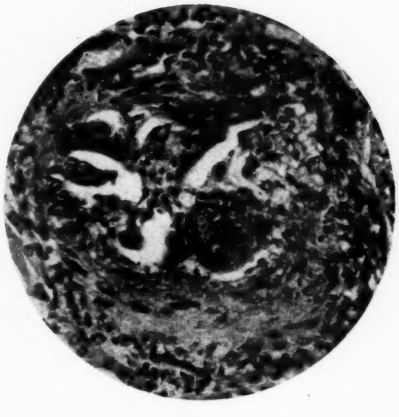


FIG. 5

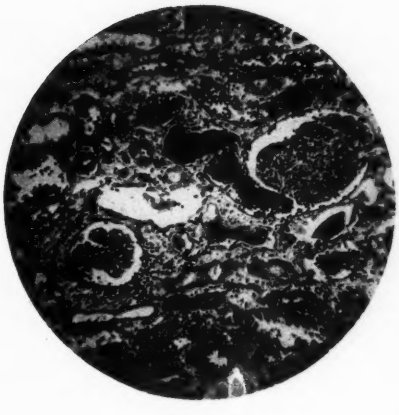


FIG. 6



FIG. 7



FIG. 8

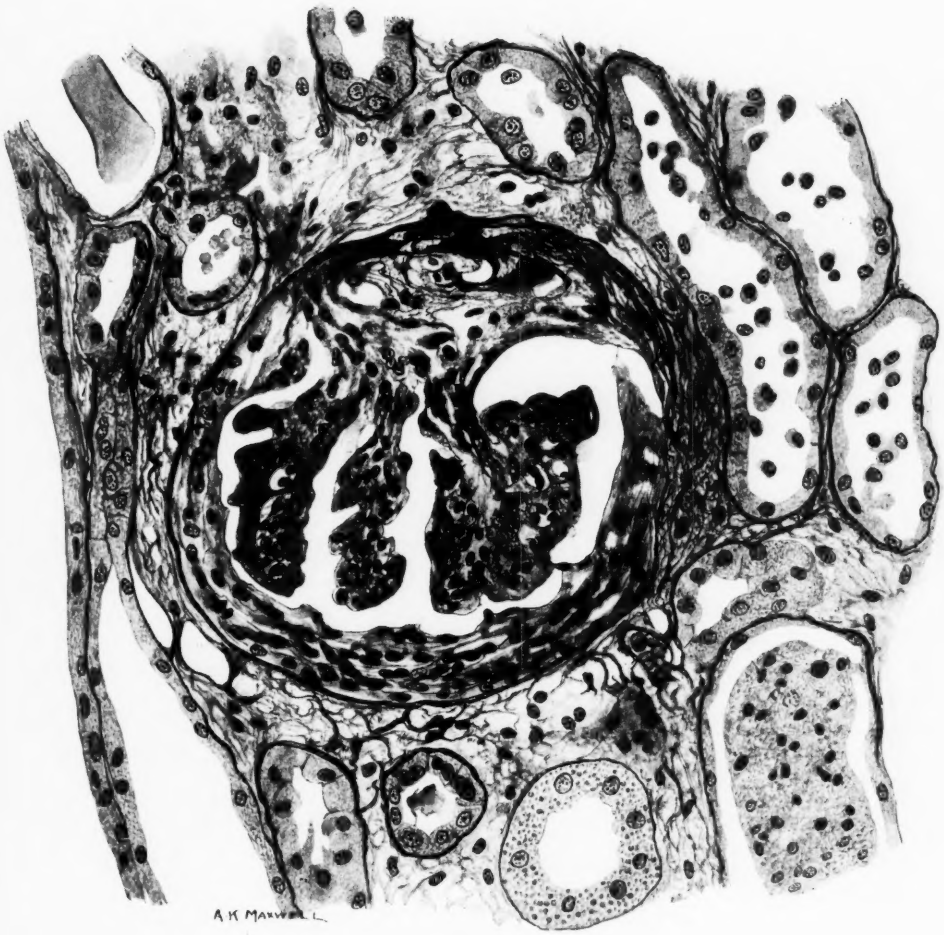


FIG. 9

GUNSHOT WOUNDS OF THE CHEST

By J. M. FORTESCUE-BRICKDALE

Gunshot injuries of the chest necessarily present a varied clinical aspect, according as they are seen at the front, at the base, or in hospitals in England.

Even at the same base, two hospitals may record different experiences, owing to their position as regards distance from the railway station or siding whence patients are transferred by ambulance to the wards. The conclusions and deductions in this paper, therefore, must be understood to apply to a base hospital in France, so situated that severe cases could be prudently sent there, but not so near the railway as some others, and, therefore, not receiving so high a proportion of evidently badly wounded men.

In this hospital 169 cases of injury to the chest came under my care and observation during the last half of the year 1916.

The following table shows the general classification of these cases, and the gross mortality (3), (7), (8):

Group.	Cases.	Deaths.	
		Number.	%
A. Haemothorax and Pneumothorax	132	6	4·5
(i) Resected cases	15	3	20
(ii) Large effusions	89	2	
(iii) Small effusions	23	1	2·5
(iv) Pneumothorax	5	0	
B. Laceration or bruising of lung	27	3	11·1
C. Non-penetrating wounds	10	0	

The patients were in most cases admitted within a week after the injury, namely:

During 1st week	149
„ 2nd „	19
„ 3rd „	1

Twenty-seven patients were admitted on the day following the infliction of the wound.

On the whole, then, the patients were seen fairly early; there was a fair proportion of severely wounded men among them, but not a large number of heavily infected cases. The proportion of non-perforating wounds is not an index of the number which arrive at the base, as many suffering from severe wounds in other parts did not come under my observation, and others who were only very superficially wounded escaped record in my series.

[Q. J. M., April, 1918.]

The following observations were made on cases of penetrating wounds, and have been arranged in sections as follows:

1. Observations on the symptoms, especially haemoptysis and fever, and the physical signs.

2. A note on the associated lung conditions, broncho-pneumonia, collapse, &c.

3. Complications, both those due to wounds of other internal organs and those due to the lesions inflicted on the lung.

4 and 5. Certain observations on the pleural fluid and blood.

6. The mortality, showing the death-rate from purely intrathoracic injury.

7. A note on a group of cases, apparently very lightly infected, in which resection was not performed.

8. A comparison between wounds produced by shell fragments and those due to bullets; tables are given showing the factors to which the higher mortality in one class of missile is due, and the peculiar dangers of each.

9. The account of the treatment adopted, and an attempt to show the results of aspiration in the non-infected cases.

Although the series is a comparatively small one, it seemed worth while to work out exact tables and percentages whenever possible, as the cases are typical of a very large group. The numerals in brackets refer to a few statistics given by other writers whose papers were accessible, whenever they could be compared with those in the present series. The references to these will be found at the end of this paper.

1. *Symptoms and Physical Signs.*

Initial symptoms. The histories obtained from patients and in some cases notes sent by medical officers at the front showed that the initial symptoms were *collapse*, which is variable, not always present, and has usually passed off by the time the patient arrives at the base; *pain*, also a variable feature and depending largely on the situation of the external wound. It affects not only the chest, but also sometimes the flank and abdomen, or the arm on the wounded side. Initial abdominal symptoms may be decidedly puzzling. In 2 cases in my series abdominal section had been performed at the Casualty Clearing Station and nothing abnormal found. The exploration wounds had healed and the patients appeared none the worse. The remaining initial symptoms are more or less *shortness of breath* (often only on exertion), *fever*, and *haemoptysis*.

The last two symptoms will now be discussed in detail.

Haemoptysis. Reliable histories were recorded in 151 cases; among these it occurred in 117, or 77·4 per cent. (3) (7). It was said to be considerable in amount in 10. In the cases in which blood or air had escaped into the pleura there was a history of haemoptysis in 71·1 per cent., and the amount was said to be considerable in 5. In 48 cases, in which the time during which fresh blood was expectorated could be ascertained, it averaged four days. In one or two cases it continued for a week or more. As a rule the amount is trifling and the

symptom needs no special treatment. Altered blood may, of course, appear in the sputum for a much longer period, but is of no import.

In 1 case haemoptysis did not come on till the third day, and in 1 it appeared on the first and third days. In 2 cases in which it had ceased it reappeared while the patients were being conveyed to the base on the ambulance train (fifth and sixth days respectively), but was not severe.

In 27 cases diagnosed as laceration or bruising of the lung, in which there were no signs of haemothorax, haemoptysis occurred in all. It continued on an average for three days, and was said to be considerable in amount in 5.

Fever. Febrile symptoms are present in the large majority of cases. Some of the cases in this series showed no fever during the time under observation, but may have had a day or two's fever before arrival at the base. There were 17 cases of sterile haemothorax, uncomplicated by other wounds or by inflammatory intrathoracic conditions in which the duration of the fever could be determined.

The average was 10 days, the maximum 23, and the minimum 2.

Under 7 days	18 cases.
8 to 14 days	20 „
15 to 21 days	7 „
Over 21 days	2 „

In 8 resected cases, with no complicating wounds or lesions elsewhere, in which the temperature fell during the time the patients were in hospital, the average duration of fever was 49 days, maximum 84, minimum 24 (3) (7).

In 16 cases of 'laceration' of the lung, the fever lasted less than seven days in 13, and never more than ten days.

In cases in which the fever is short, it is seldom above 100° F., except perhaps on the day after the wound, and it falls steadily. In more protracted cases it usually remains between normal and 99° F. in the morning, and 100° to 101° F. in the evening. In some cases there are marked oscillations, 99° F. in the morning, and 102° to 103° F. in the evening, and the course is very irregular. Others, again, show a low type of irregular fever with only a degree of variation for more than a week.

Physical signs. The physical signs of haemothorax are usually quite distinctive and need no special comment. They may be confirmed by X-ray examinations and exploratory puncture. Signs of overaction in the unaffected portions of the lungs may often be found. Harsh compensatory breath-sounds may be observed over the front of the chest on the affected side, and in front or behind on the opposite side. The resonance in front of the chest is sometimes increased either on the side of the haemothorax or on the opposite side, and the praecordial dullness and cardiac impulse may be obliterated or very difficult to determine.

In 2 cases I observed on the eleventh and thirteenth days respectively a short puff at the end of expiration, occurring about the middle of the back on

the affected side. It suggested a small localized cavity in the pleura, communicating with the lung.

The presence of Grocco's paravertebral triangle of dullness was not systematically determined. It was noted as present in 12 cases, in 3 of which there was only a small amount of blood effused.

In 18 cases of pneumothorax or pneumo-haemothorax the physical signs occurred as follows:

Resonance.	Tympanitic	7
	Much increased	2
	Increased	9
Breath-sounds.	Amphoric	1
	Very faint	4
	Absent	13
Tactile vocal fremitus.	Very faint	4
	Absent	7
	Present	7
Vocal resonance.	Unaltered	18
Bell-sound.	Present	2
	Absent	16

The last-named sign was also present in one case after a considerable amount of oxygen had been run in to replace a haemothorax.

In 10 cases the physical signs were not distinctive, but on aspiration air mixed with blood was evacuated.

2. *Associated Lung Conditions.*

In 1 case there was a history of severe bronchitis with muco-purulent expectoration. The physical signs of bronchitis of a mild type were observed in 20 cases. Cough and expectoration were common. In 6 cases the bronchitis was associated with signs of pleurisy, in 19 pleurisy occurred alone. In 2 of these there was pleuritic effusion.

Case 1. Admitted on the third day after a perforating rifle-bullet wound of the left chest. Ninth day: 17 oz. of blood aspirated. Eleventh day: rise of temperature and left-sided pleurisy. Fourteenth day: signs of pleural effusion, which two days later broke through the old exit wound made by the bullet. It was not purulent at first, but infection rapidly occurred, necessitating resection.

Case 26. Admitted on fifth day after penetrating rifle-bullet wound of right chest. Twelfth day: aspirated—a large amount of air and some clear serous effusion withdrawn.

The physical signs disappeared with the exception of poor air entry at the right base by the twenty-first day. Temperature fell by lysis, becoming normal on the sixteenth day.

Pneumonia or broncho-pneumonia occurred in 3 cases. One was a case of general septic infection and ended in death (see Appendix, Case 14).

The two other patients recovered. In one the pneumonia affected the side opposite the haemothorax (which had been aspirated), and began on the twelfth day after the wound. In the other a rifle bullet had entered the chest without producing a haemothorax; a severe type of septic pneumonia supervened, affecting both lungs, and the temperature did not become normal till the thirty-third day.

One case of gangrene of the lung, without haemothorax, occurred and was fatal (see Appendix, Case 158).

Breath-sounds may be noticed to be weak in the front of the chest on the same side as the haemothorax or at the base on the opposite side. In 18 of the cases in this series there were definite signs of collapse of the lung. The following showed an alteration in the physical signs during its course. In the rest they remained the same in character throughout.

Case 138. Admitted on fourth day after revolver-bullet wound in third intercostal space, anterior axillary line on the right side. Seventh day: dullness, bronchial breathing, diminished vocal fremitus, and vocal resonance over the right base behind. Eighth day: no breath-sounds heard over the lower part of the dull area. Soft breath-sounds over the upper part. Twelfth day: physical signs cleared up. Temperature normal throughout.

11 of these cases occurred during the first week and 7 during the second. No signs of collapse were observed later than the thirteenth day.

The wound was near the diaphragm in 6 (6) cases, not near the diaphragm in 12. In 10 collapse occurred on the same side as the wound and in 8 on the opposite side.

	Wound on R. side.	Wound on L. side.
Collapse on same side . .	8	2
„ opposite side .	5	3

The cardiac impulse was not observed to be drawn over towards the collapsed side in any of these cases, but in 2 it was pushed over towards the opposite side. The reason for this is not apparent.

Case 130. Admitted on first day after a shrapnel wound on the right side of the back. Slight initial haemoptysis. Third day: dullness, absent. Vocal fremitus and very faint breath-sounds over the right base. Cardiac impulse and dullness just beyond the nipple line in fifth space. Eighth day: right base and heart normal, no sign of haemothorax by X-ray examination, diaphragm moving normally, no cardiac displacement.

Case 141. Admitted on first day after a shrapnel wound over the right shoulder. Exit wound in mid-dorsal region over the spine. Third day: poor note and very weak breath-sounds at the right base. Cardiac impulse and dullness in nipple line fifth space. X-ray examinations showed no signs of haemothorax. Temperature normal.

Congestion. In 4 cases there were physical signs of congestion at the base of the lung, without fever or other inflammatory phenomena. In 3 the physical signs were at the left base, the wounds being on the right side of the chest. In 2 a haemothorax was present. The signs were found on the sixth or seventh

day and lasted from three to seven days. In the fourth case the wound was on the left side; there was no haemothorax, and no fever after the first day. Dullness, râles, and poor air entry were observed at both bases on the third day, and the physical signs cleared up by the twelfth day.

3. *Complications.*

Jaundice was observed in 2 cases.

Case 3. Admitted on the second day after a shrapnel wound of the right chest with a large haemothorax. The projectile was not seen either above or below the diaphragm by the X-rays. Fifth day: slight jaundice and urticaria. The jaundice deepened till the eighth day, after which it gradually faded. The liver was explored under an anaesthetic, but nothing was found. The haemothorax was reported infected with streptococci, and subsequently a rib was resected.

Case 125. In this case there was an anaerobic infection and wound of the liver. The patient died (see Appendix, Case 125).

The following case came under my observation at another time and is not included in the series:

The patient was admitted on the fifth day after a shrapnel wound of right chest, a wound below the costal margin on the right side of the back, and a deep lacerated wound of the right thigh. X-rays examinations showed a shrapnel ball lying superficially near the second right costal cartilage and fragments of shell-casing in the right lung one inch above the diaphragm. There were physical signs of fluid at the right base, but only a slight shadow. Clear, slightly blood-stained fluid was withdrawn and found to be sterile. Eighth day: slight epistaxis. Ninth day: severe and continued vomiting. Slight jaundice, no bile pigments in the urine. Tenth day: still vomiting. Jaundice deeper. Patient very weak and ill. Eleventh day: less vomiting. No bile pigments in urine. Twelfth day: patient became collapsed and died in the afternoon. Post-mortem: localized suppurative pleurisy under the bullet. Pleural effusion over base of right lower lobe. The missile entering at the wound in the back had wounded the right kidney, but not the liver.

The jaundice, therefore, is not the result of gross damage to the liver, but is of the toxic type.

Abdominal injuries. Occurred in 3 cases, and were fatal (see Appendix, Cases 15, 125, 157).

In 2 cases the liver was wounded but the patient survived. In one there was a discharge of bile from a wound in the right side, which ceased after a few days; in the other a foreign body was seen by the X-ray embedded in the liver, but gave rise to no symptoms.

Lesions of the nervous system were noted in 4 cases. In 2 the spinal cord was damaged, producing paraplegia; in 2 there were peripheral nerve injuries producing paresis of the right arm.

Haematuria occurred in 1 case.

Case 29. Admitted on the fourth day after a shrapnel-bullet wound which had entered the chest near the angle of the tenth rib on the left side, and passing

upwards had left it at a point over the fourth intercostal space, about two inches outside the nipple line. Haemothorax present and aspirated. Staphylococci found in the pleural blood. Tenth and eleventh days: haematuria. A catheter specimen was found to be normal in other respects and sterile. Fourteenth day: temperature 101·4° F. Fifteenth day: temperature fell to normal. No further symptoms.[1]

It is difficult to see how the bullet could have wounded the kidney, and, even if it did, why the haemorrhage occurred on the tenth day (8).

Subcutaneous emphysema was noted in 21 cases. In 9 it was small in extent, moderate in 6, and extensive in 4 (in 2 cases the projectile did not appear to have penetrated the thorax); in 2 cases it was very extensive. The symptoms cleared up rapidly (3).

Secondary haemorrhage. In 6 cases in which a haemothorax was aspirated on the second or third day, there was evidence that further bleeding may have occurred in one instance.

(i) Admitted collapsed to a Casualty Clearing Station and 26 oz. aspirated on the next day. Transferred to the base on the seventh day with signs of a large haemothorax. 64 oz. aspirated on the tenth day. The fluid was thick, of a reddish-brown colour, showed no distinguishable cells under the microscope, and was sterile.

(ii) Aspirated at a Casualty Clearing Station eighty-four hours after being wounded. Transferred to base on the ninth day with signs of a large haemothorax. 24 oz. aspirated on the fifteenth day. The fluid was thin and blood-stained, showed sedimentation, but did not coagulate. It contained endothelial plaques, but no recognizable blood-cells, and was sterile.

(iii) 49 oz. aspirated at a Casualty Clearing Station on the third day. Transferred to base on the eighth day, when physical signs were so slight that no further aspiration seemed necessary.

(iv, v) Two cases aspirated at the base on the third day without signs of reaccumulation.

(vi) 36 oz. aspirated at the base on the second day. Cardiac impulse then found to be one inch *outside* the nipple line. Fifth day: cardiac impulse one inch *inside* the nipple line. Eleventh day: cardiac impulse again one inch *outside* the nipple line. Fourteenth day: cardiac impulse returned to nipple line. The physical signs over the right base remained unchanged throughout.

In the first 2 cases the blood was altered, and there was no evidence that bleeding had occurred after the primary puncture. In the third, fourth, and fifth no bleeding of any consequence can have occurred. In the sixth it seemed probable that further haemorrhage took place, but it ceased fairly soon, as on the nineteenth day only 10 oz. could be withdrawn owing to clotting.

[1] The subsequent history obtained by the Medical Research Committee gave no indication of a recurrence of the haematuria, and the patient returned to duty 2½ months after he was wounded.

4. *Character of the Pleural Fluid.*

The fluid withdrawn from the pleura by aspiration varies in appearance from what seems like normally clotting blood to a thick brownish-red fluid, from which a deposit forms on standing, leaving a bright yellow serum. In these specimens clotting is absent or very slow and imperfect. In other cases a thin blood-stained serum is withdrawn. Effusions infected with anaerobic organisms have a characteristic unpleasant odour.

In 4 specimens from which anaerobes were isolated the following characters were noted. In 1 the fluid was thin and coagulated rapidly, in 3 others it deposited a thick sediment and clotted incompletely or not at all. One aspirated on the third day showed 64 per cent. polynuclear cells ; a second, in which there was a mixed infection of anaerobes and cocci, showed an excess of polynuclear cells on three occasions. The remaining 2 showed almost entirely lymphocytes.

In 5 specimens infected by various cocci in which the behaviour of the fluid as to clotting was noted, in 4 coagulation took place imperfectly or slowly, and in 1 it was rapid. In 9 specimens, all but 1 showed an excess of polynuclear cells; the remaining 1, explored on the eighth day, showed only a few lymphocytes and no other cells.

In 20 specimens which were found to be sterile clotting was noted in 2 cases as rapid ; in 6 others it was imperfect or absent, often with sedimentation. In those aspirated during the first nine days, polynuclear cells were in considerable excess in 8, and in 8 more constituted about 50 per cent. of the total. In 7 the lymphocytes were considerably in excess. On the other hand, in the specimens taken from patients aspirated from the tenth to the twentieth day lymphocytes were in excess in 5 and in equal numbers to the polynuclears in 2 ; in none was there an excess of polynuclear cells.

Cells in proportion of 50 % and upwards	4th to 9th day	10th to 20th day
Polynuclears	70 % of specimens	30 % of specimens
Lymphocytes	30 % of specimens	70 % of specimens

Endothelial cells were noted in 37 out of 63 specimens in varying numbers, which bore no apparent relation to the infection or non-infection of the pleural fluid, or to the date after the injury on which the specimen was obtained.

5. *Blood Counts.*

Differential leucocyte counts were made in a few cases (19).

In 7 cases of haemothorax without complicating factors (such as other wounds or chest affections) there was a relative increase in the small lymphocytes and a decrease in the polynuclear cells towards the end of the first week, together with a decided increase in the eosinophil cells, and a less marked increase in the basophil granular cells. In two cases of infected haemothorax, which were subsequently resected, these features did not appear to the same extent, and were later in developing.

In a case of non-penetrating wound of the chest, which was examined as a control, these changes could not be traced. In one of the cases where the eosinophilia was excessive the patient developed at the same time an urticarial rash, which was attributed to the antitetanic serum. All the patients had received one dose of serum on the day of the wound.

Averages of Blood Counts.

GROUP I. *Infected Haemothorax.*

	Day after wound.								
	2	3	4	5	6	7	8	9	10
Polynuclear		86		79	88	73	67	65	77
Lymphocytes		12		13	10	20	27	23	17
Transitionals		1		4	0·6	2	2	2	1
Large mononuclear		1		4	0·1	3	1	4	2
Total mononuclear		14		21	1·0	25	30	29	20
Eosinophils		0		0	9	0·6	0·4	0·6	0·6
Basophils		0·2		0	0	0·5	0	0·6	0·3

GROUP II. *Non-infected Haemothorax.*

	2	3	4	5	6	7	8	9	10	12	15
Polynuclear	77	69	64	57	53	61	64	56	60	68	67
Lymphocytes	18	21	24	32	33	30	24	34	29	28	27
Transitionals	2	2	2	1	1	1	2	1	2	2	1
Large mononuclear	2	2	0·6	2	2	1	—	2	1	1	1
Total mononuclear	22	25	26	35	36	32	26	37	32	31	29
Eosinophils	1	3·5	4·5	4·6	4·6	6·2	5·4	4·6	4·1	1·8	1·7
Basophils	0	0	0·3	0·1	0·6	0·3	0·1	0·4	0·8	0·4	0·5

Control Case. Non-penetrating wound.

	3	4	5	6	7	8	9
Polynuclear	65	66	73	67	66	69	71
Lymphocytes	33	29	23	29	32	28	24
Transitional	0·5	2	1	1	1	1	1
Large mononuclear	1	0·8	1	2	0·6	1	2
Total mononuclear	33	31	25	32	33	30	27
Eosinophils	0	0·6	1·0	0·7	0·4	0·3	0·1
Basophils	0	0	0	0·3	0	0	1

The remaining cases have not been quoted, as in some complicating factors were present, and in others the counts were not systematically made over a sufficient number of days.

6. *Mortality.*

The gross mortality of 159 penetrating wounds of the chest was 9, or 5·6 per cent., but not all of these patients died of thoracic injuries. In 2 cases with haemothorax there were severe concomitant abdominal injuries, and in 2 cases without haemothorax there was a severe abdominal injury in one, and a septic meningitis in the other. In 1 case of haemothorax the external wound was infected by gas-producing organisms. The deaths, therefore, which were attributable to purely intrathoracic injuries were 4 in number, or 2·5 per cent. of the total number of cases. This includes one patient who died of septic pericarditis and pleurisy.

Group.	Cases.	Deaths.	
		Number.	%
A. Haemothorax and pneumothorax	132	4	3
(i) Resected cases	15	2	13·3
(ii) Large effusions	89	1	
(iii) Small effusions	23	0	0·8
(iv) Pneumothorax	5	0	
B. Laceration or bruising of the lung	27	1	3·7

All the 9 deaths which occurred in the entire series except 1 were due to septic infection. 4 were caused by anaerobes, 1 by a number of organisms of which the pneumococcus was the predominant, and in 2 the causal organism was not determined. In the 1 case in which sepsis was not a factor the patient died of intra-abdominal haemorrhage.

In 20 severely infected cases there were four (8) (3) (7) deaths from purely intrathoracic causes (20 per cent.).

Short notes of all the fatal cases will be found in the Appendix.

7. *Lightly-infected Cases.*

In 29 cases organisms were grown from the blood, but resection was not performed in France. The organisms were:

Staphylococcus albus	19 cases
Gram-negative diplococci	2 „
Anaerobic organisms	5 „
Streptococci	2 „
A coliform organism	1 „

1. *Staphylococcus albus.* In 9 cases the absence of fever and of general symptoms made it appear that the organism was only an accidental contamination. In 2 others complications accounted for the fever, which subsided when these were dealt with. The after-history of 9 out of the 11 cases was traced by the Medical Research Committee in England, and in no case was there any record of further operations on the chest. Seven had returned to duty either in France or at their depôts at the time of the inquiry.

In 8 of the cases there were more pronounced symptoms, suggesting an infection of the pleural fluid.

In 2 there was a slight rise of temperature about the tenth day after the wound; both these cases were aspirated in France. The Medical Research Committee's report on the after-history of 1 showed that no further treatment for the chest condition was necessary, and that the patient remained in hospital 2¾ months in all before returning to duty. The other case was still in hospital eleven months after the wound, but no medical case-sheet could be obtained.

In 2 cases the fever lasted sixteen and eighteen days respectively, but was never high, and fell steadily without much oscillation. Both were explored twice, but only a small amount of blood was withdrawn. They remained in hospital in England for about one month and were discharged to duty without further operations on the chest.

In the remaining 4 cases the temperature remained high for a considerable period. The charts of these cases are appended (Charts 1 to 4).

(i) Thirty-two days' fever of an oscillating type. Aspirated 11 oz. on the fifth day, some air also being withdrawn; on the eighteenth day further exploration. On each occasion the organism was cultivated from the pleural blood. Two tests for enteric agglutinins were made with negative results. There was slight leucocytosis on the twenty-second day (W. B. C. 12,000). The Medical Research Committee's report showed that he was discharged from the army as unfit after a total of four months in hospital, but there was no record of any subsequent operation on the chest in England.

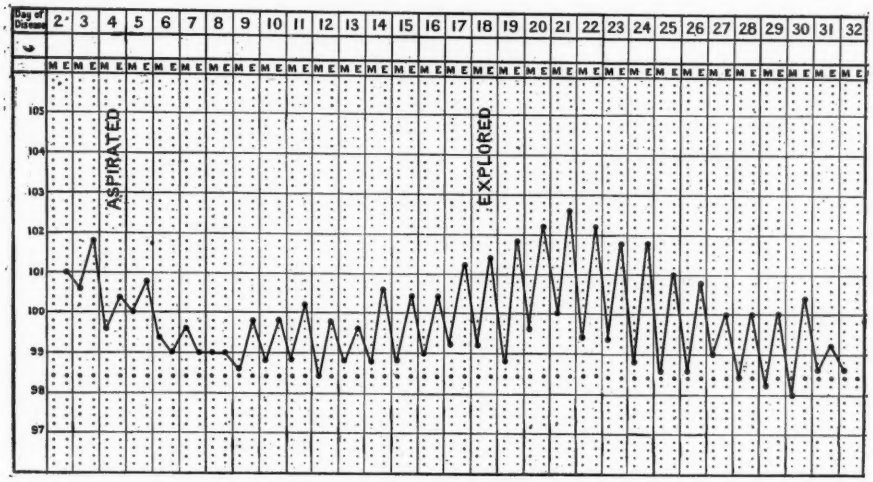


CHART 1 (Case 38).

(ii) Fifty days' fever of an oscillating type. Aspirated 24 oz. on the sixth day. Explored at various points on the chest on the sixteenth and nineteenth days, without aspiration. On the thirty-sixth day 2 oz. only could be withdrawn. S. albus cultivated on three occasions. The patient's general condition was good throughout, as he slept and ate well, but his mental condition was childish, and several times he had incontinence of urine. Four months after his wound the chest condition was reported as satisfactory; there had been no return of fever, but his mental condition was unchanged.

(iii) Thirty days' fever. Aspirated 56 oz. on the seventh day, and again explored on the twentieth day. The organism was only found once. The Medical Research Committee's report showed that he remained 2¼ months in hospital and was discharged to duty in England without further operation.

(iv) Twenty days' fever of an oscillating type. Aspirated 26 oz. on the fifth day and 2 oz. on the twelfth day. The organism was cultivated from the fluid on both occasions. He was discharged to duty in England after 2½ months, without further operation.

In these 4 cases the projectile was only retained in the chest in 1 (Case ii).

Gram-negative diplococci. In the 2 cases where these were found the organisms appeared to be merely contaminations. There was no clinical

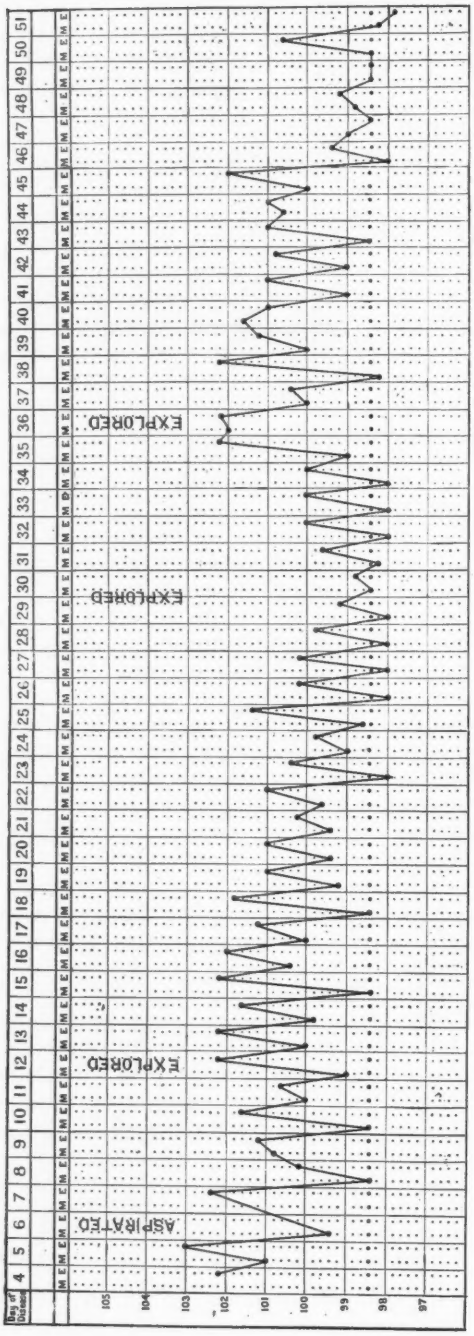


CHART 2 (Case 46).

evidence of an infection, and their subsequent history after evacuation to England showed that they were both returned to duty without further symptoms.

Coliform organism. The evidence of infected haemothorax was not at all conclusive, and after evacuation to England the patient was discharged without further operative treatment and was classed fit for general service.

Anaerobes. In these 5 cases only 1 had fifteen days' fever. In 3 the fever was of still shorter duration, and in 1 there was no fever at all.

The Medical Research Committee's report showed that all were returned to duty in two to three months without further operation, and that 3 were serving in France.

Streptococci. (i) The patient had an oscillating temperature for three weeks, sometimes reaching 102° F. in the evening, which fell gradually after each aspiration (eleventh and fourteenth days). Pus cells and streptococci were present on the first occasion, pus cells only on the second. His general condition was fairly good when he was evacuated to England.

(ii) The patient had an oscillating temperature for thirty-three days, mainly apparently due to infection of the external wound.

Aspiration on the sixteenth day did not affect the course of the fever; streptococci were found in the fluid. When the external wound was opened up the temperature fell; no communication with the pleura was then found.

Unfortunately the after-history of these 2 cases could not be traced (6).

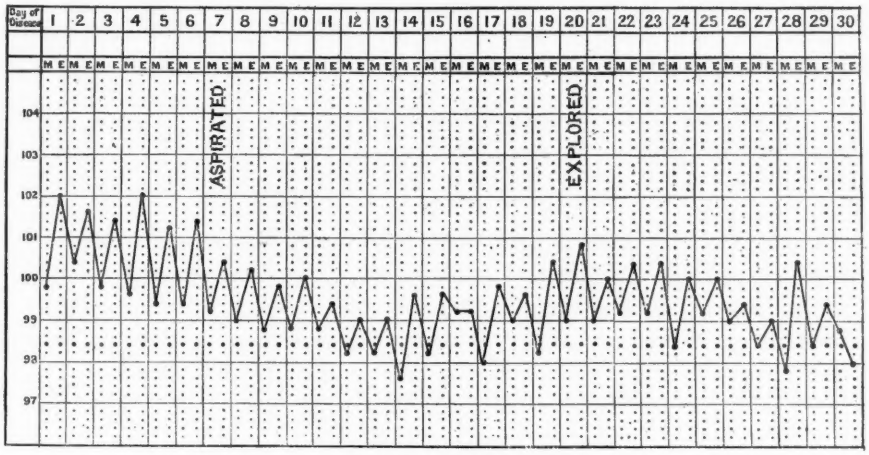


CHART 3 (Case 62).

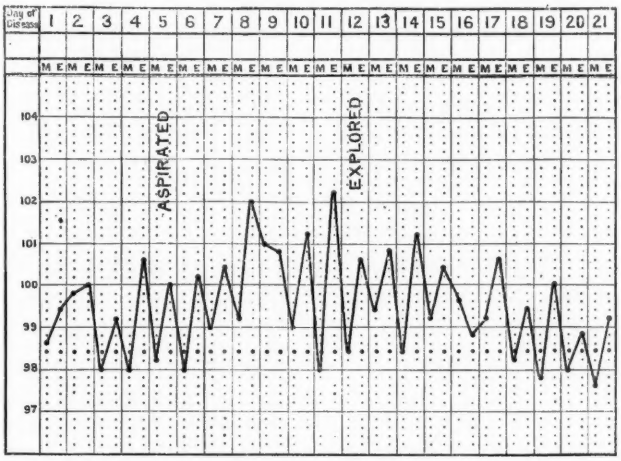


CHART 4 (Case 52).

8. *Comparison between Shell-fragment and Bullet Wounds.*

In 143 cases of penetrating wounds of the chest the nature of the projectile was ascertained (3).

Bullets, 47 . . . . . = 32·9 per cent.
Shell fragments, 95 . . . . = 66·4 „
Aerial dart, 1 . . . . . = 0·7 „

In 47 cases of bullet wound there were two deaths = 4·2 per cent.

In 93 cases of shell-fragment wound there five deaths = 5·3 per cent.

In 137 cases the retention or non-retention of the projectile was recorded.

Projectile.	Retained.			Not retained.		
	Cases.	Deaths.	%	Cases.	Deaths.	%
Bullets	15	0	—	29	2	6·8
Shell fragments	49	4	8·1	44	1	2·2

71 per cent. of the total deaths in which the projectile was known were caused by shell fragments.

In every 100 cases there will be 4·6 deaths—3·3 due to shell fragments and 1·3 to bullets.

Shell fragments, therefore, are somewhat more fatal than bullets, although bullets more often produce perforating wounds. In 51 cases of perforating wound 29 were due to bullets. The retained bullet is not so fatal as the retained shell fragment, though the bullet which is not retained is more fatal than the shell fragment which is not retained.

This can be explained by a consideration of the separate factors involved.

1. *Sepsis.* In 14 cases requiring resection (that is, obviously heavily infected), 10 were caused by shell fragments and 4 by bullet wounds, and of 6 deaths from sepsis, 4 were caused by shell fragments and 2 by bullets. In 28 cases of haemothorax in which organisms were grown from the fluid withdrawn by exploration, 23 were due to shell fragments and 5 to bullets. In 12 of these there was presumably a certain degree of sepsis, as the febrile symptoms were well marked. 8 of the 12 were due to shell fragments, and in 2 the shell fragment was retained.

The following table shows the organisms found and the projectile concerned :

Organism.	Shell Fragments.		Bullets.	
	Retained.	Not retained.	Retained.	Not retained.
Staphylococcus albus	—	4	1	1
Streptococcus	—	1	—	—
Anaerobic organisms	2	1	1	1
Totals	2	6	2	2

2. *Haemoptysis.* As a possible indication of the direct damage caused to the lung by the different forms of projectile, the following analysis of the cases showing this symptom was made.

In 114 cases of haemothorax 35 were caused by bullet wounds, 79 by shell fragments, and there were 85 cases of haemoptysis. In a proportion of these the length of time during which the haemoptysis lasted could be ascertained.

Projectile.	Haemoptysis.		Average continuance in days.	Maximum duration in days.	Cases in which considerable.
	Number of Cases.	%			
Bullets	28	79·4	5·8	12	1
Shell fragments	57	72·1	3	9	3

In 24 cases of penetrating wound without haemothorax 8 were caused by bullets and 16 by shell fragments, and haemoptysis occurred in all.

Projectile.	Haemoptysis. Number of Cases.	Haemoptysis. %	Average continuance in days.	Maximum duration in days.	Cases in which considerable.
Bullets	8	100	3·2	9	2
Shell fragments	16	100	3·7	8	3

Combining these two tables, bullet wounds cause haemoptysis in 83·7 per cent. of cases, it is considerable in amount in 7 per cent., and continues on an average for four days. Shrapnel wounds cause haemoptysis in 74·7 per cent. of cases, it is considerable in amount in 6·5 per cent., and continues on an average for three days.

3. *Duration of fever.* The nature of the projectile does not seem to affect the duration of the fever in uncomplicated cases. In 32 cases of sterile haemothorax, the average duration of fever was ten days in the case of both bullets and shell fragments; and in 13 cases of 'laceration' of the lung, the average duration was eight days for bullets and 7·6 for shell fragments.

4. *Associated lung conditions.* In 48 cases in which some inflammatory condition of the lungs or pleura, giving rise to definite physical signs, was noted, 13 were caused by bullets, 29 by shell fragments, and in 6 the projectile was not ascertained.

Disease.	Number of Cases.	Bullets. Number.	Bullets. %	Shell Fragments. Number.	Shell Fragments. %
Bronchitis	20	5	25	15	75
Pleurisy	5	0	0	5	100
Bronchitis and pleurisy	15	6	40	9	60
Pneumonia and broncho-pneumonia	2	2	100	0	0
Totals	42	13	31	29	69

5. *Leaking wounds.* In 7 cases in which there were leaking wounds on admission, 3 were caused by bullets and 4 by shell fragments.

6. *Perforating wounds.* In 51 perforating wounds, 29 were caused by bullets, 19 by shell fragments, and 3 by projectiles the description of which was unknown. 67 per cent., therefore, of the bullets perforated the chest, and 20 per cent. of the shell fragments.

Summary. Shell fragments are accountable for a somewhat higher mortality than bullets. This is due to the greater likelihood of septic infection. In five-sevenths (71 per cent.) of the resected cases (i. e. those heavily infected) the wounds were caused by shell fragments. 66 per cent. of the cases where a light infection occurred were due to shell fragments, and 57 per cent. of leaking wounds, which are, of course, more liable to infection. 69 per cent. of the cases in which inflammatory conditions in the thorax were observed were due to shell-fragment wounds.

On the other hand, bullets caused a greater number of perforating wounds, and produced more haemoptysis.

In uncomplicated sterile cases the fever was of the same duration in both classes of wounds.

9. *Treatment.*

Heavily infected cases. When the fluid withdrawn by the exploring syringe is found to contain numerous bacilli, streptococci, or pus cells, the ordinary surgical treatment for an empyema is necessary. In many cases it is not needful to wait for the result of a laboratory examination, as the obvious characters of the fluid, and especially its odour, are sufficient to show that it is septic. At the operation, or at subsequent dressings, clots should be removed and the pleura irrigated. When the projectile is easily accessible, it should, of course, be removed, but extensive operations are not advisable. The following case, however, in which the foreign body was not found while the patient was in France, is instructive:

Case 8. Admitted on fourth day after a shrapnel wound on right shoulder, just over apex of lung. There was a large pneumo-haemothorax on the right side, with much cardiac displacement. The temperature oscillated between 99° F. and 101° F. Ninth day: aspiration, only 6 oz. of rapidly clotting blood withdrawn. The fever continued and the patient suffered from rather severe joint-pains of a rheumatic type. Thirty-first day: aspiration, 44 oz. of dark brown blood mixed with air. The fever continued and there were indefinite abdominal symptoms. The foreign body was located near the diaphragm, but there was some doubt as to whether it was above or below. Forty-second day: the pleura was opened and a large amount of foul blood and clot removed. The patient's general condition improved and the temperature became normal on the eighty-fifth day. He was evacuated to England, but it was subsequently learnt that on closure of the empyema wound the febrile symptoms returned, and an operation for the removal of the foreign body was undertaken, after which the patient recovered.

In 2 cases of anaerobic infection, attempts were made by repeated aspiration and the injection of oxygen to obviate the necessity for resection. In 1, in which the patient's condition remained fairly good, the chest was aspirated eight times during six weeks, a total of 190 oz. being removed. The temperature, however, only fell temporarily after the aspirations, and bacteriological examinations showed that though the anaerobes gradually disappeared from the fluid, Gram-positive diplococci remained and increased in numbers. On the fifty-fourth day resection was performed and the patient made a good recovery. In the second case, the chest was aspirated three times in twenty-six days, a total of 162 oz. being removed. On the last occasion the fluid was purulent, and a rib was subsequently resected. The patient, who was extremely ill on admission, made a good recovery.

Lightly infected cases. In this class of case, though organisms are found in the blood withdrawn by exploration of the pleura, the patient's general condition does not suggest a severe infection. These cases may be treated in the same way as those which are bacteriologically sterile, but they require careful watching, and often repeated exploration, as in some the infection becomes more

severe, definite pus appears in the pleura, and resection becomes necessary. Even where the fever persists for a long time these patients eventually recover, with good functional restoration in the lung, if the organism is a staphylococcus.

Sterile cases. In simple sterile haemothorax the treatment will depend on the size of the effusion and its effects on the position of the heart and the general comfort of the patient. These are not solely dependent on the number of ounces of blood in the pleura; some patients tolerate much larger collections of fluid without obvious inconvenience than others.

It is not necessary to keep the patient absolutely immobilized, though he should of course be kept strictly to bed. Most patients prefer to be propped up for all or part of the time.

Except cases in which an exploratory puncture shows that the blood has clotted and cannot be withdrawn, it is advisable to aspirate about the end of the first week. In 89 cases in which there was evidence of a fair-sized effusion, an average of 26 oz. was removed from 64. The minimum amount was 10 oz. and the maximum 76 oz. Of the remaining 25 cases, 1 died of anaerobic infection before any attempt at aspiration could be made, 1 had already been aspirated at a C. C. S. before admission, and 1 was transferred to England without aspiration. In the remaining 22 cases, 10 were cases of pneumo-haemothorax from which air and a small quantity of blood were removed. In the rest, clotting interfered with aspiration; in only 4 of them was it attempted during the first week.

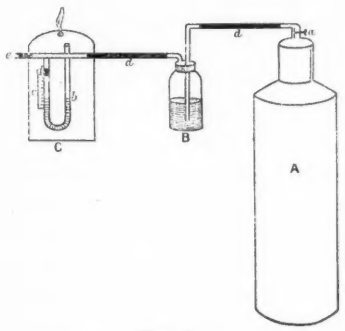


FIG. 1.

A. Oxylite.
B. Wash-bottle containing absolute alcohol.
C. Board on which manometer is fastened.
a. Tap.
b. Manometer.
c. Millimetre scale.
d,d,d. India-rubber tubing.
e. Tubing leading to needle.

A general anaesthetic was not found necessary except in a few cases. The skin was frozen for the insertion of the trocar and cannula. Potain's apparatus was used. Oxygen replacement was adopted in all cases, and seemed decidedly useful. Three or four pints could be removed without coughing or respiratory distress to the patient. The oxygen was generated in a convenient French apparatus known as the 'Oxylite', passed through a wash-bottle containing absolute alcohol, and then over a manometer. The tubing through which it passed was boiled and connected with the apparatus immediately before use. The needle connected with the oxygen tube was of fairly wide bore, and was inserted two or three spaces above the Potain cannula; the oxygen was allowed to flow in at a pressure of not more than 3 or 4 mm. during the aspiration, and sometimes for a few minutes longer. Often some bubbled out with the last 2 or 3 oz. of blood. The advantage of the 'Oxylite' generator is that the

gas is given off at comparatively low pressure and is easy to control by means of the tap at the top of the cylinder.

The general arrangement of the apparatus is shown in the figure. In 9 cases, small amounts of eusol (10 to 15 c.c.) were injected after the aspiration, but with no appreciable effect on the temperature or other symptoms. A second aspiration was not usually attempted, though in some cases an exploratory puncture was made if the physical signs or fever persisted. In most cases the intrapleural blood had clotted. In 9, however, the pleura was aspirated for a second time. In 5 only a small quantity was drawn off; in 3 one to three pints were removed; and in the last, one pint, after the first aspiration had yielded only a small quantity.

Cases may occur in which there are signs of a large effusion, and yet aspiration fails to draw off the blood. Unless the patient is much distressed, these cases do quite well if left alone, but recover more slowly. If there is much dyspnoea and distress the pleura may be opened under an anaesthetic, the blood and clot turned out, and the opening closed. These cases should not be treated as an empyema.

In one case in this series, where a drainage-tube was inserted, the pleura rapidly became infected and the patient died (Appendix, Case 13) (2).

In this series of cases no attempt was made to recover the foreign body, unless it was easily accessible, either in the chest-wall or the pleura. It seems very doubtful if any real advantage is gained by extensive operations on the lung for the removal of bullets or shrapnel fragments, unless there is a definite evidence that they are septic, and producing abscess or gangrene of the lung. Where there are no signs of this, the foreign body is probably harmless.

The immediate results of aspiration are all that can be described at present. As to the remote results further evidence will be forthcoming later on.

Even when the haemothorax is not causing actual dyspnoea, the patient is always more comfortable after the fluid has been removed, and for this reason only it is worth while to aspirate whenever possible. After aspiration the temperature may rise slightly for a day or two and then fall to normal, or it may show a decided fall; but more often it appears to be entirely uninfluenced. The following observations showed the results as regards the functional activity of the lung and the position of the heart as far as these were noted during the period in which the patients remained in France.

Haemothorax. 51 cases aspirated.

9 showed no change in physical signs of air entry when examined between the fourth and thirteenth days after injury.

34 showed improved air entry. First week 3 cases, second week 16 cases, third week 12 cases, after third week 3 cases.

2 showed much improved air entry when examined on the eighteenth and forty-third days after injury.

6 showed practically normal air entry; first week 1 case, second week 4 cases, fourth week 1 case.

11 cases not aspirated.

8 showed no change in air entry when examined on tenth and thirty-ninth days after injury.

2 showed improved air entry, 1 in the third and 1 in the fourth week.

1 showed much improved air entry on twenty-seventh day.

60 per cent. of the aspirated cases thus showed improvement in the first three weeks, and 10 per cent. were practically normal in a fortnight. In the non-aspirated cases there were only 27 per cent. which showed any improvement in four weeks.

In the 5 cases which recovered rapidly the wounds were at the apex in 2, at the base in 2, and in the middle of the chest in 1 (1).

In 20 cases in which the heart was displaced, as shown by physical examination, the X-rays, or both, the following results were observed:

Right side. Average amount withdrawn, 36 oz. Heart normal in four to fifteen days in 10 cases; heart not normal in two to nine days in 4 cases.

Left side. Average amount withdrawn, 31 oz. Heart normal in 3 cases in five, twelve, and twenty days; heart not normal in 2 cases in twelve and nineteen days.

In 60 per cent. of the cases, therefore, the heart had returned to its normal position within a fortnight. In 1 case which was not aspirated the heart was normal in position in three weeks.

Pneumo-haemothorax.

Right side. In 5 cases the cardiac impulse was in the nipple line or ½ to 1 inch outside it. In 2 cases which were aspirated the heart was normal within a fortnight, in 3 cases which were not aspirated the heart was normal in seventeen days.

Left side. In 4 cases showing much cardiac displacement to the right by X-rays, in 1 the heart was normal in a fortnight, and in 1 in about four weeks. In the other 2 it was not normal in a fortnight. All had been aspirated.

In pneumo-haemothorax, therefore, there is not much evidence that aspiration hastens the return of the heart to its normal position.

APPENDIX.

Fatal Cases.

Case 13. Wounded 10/6/16, admitted 11/6/16 with shrapnel wound, chest. Large right-sided pneumo-haemothorax. Heart pushed over to left. Was explored twice in several places without results. 17/6/16. Rib resected and large amount of blood evacuated. Patient's temperature, which before the operation had ranged from 99° to 101°, rose to 103°, and fluctuated between that and normal. The general condition became steadily worse and there was copious discharge of blood from the pleura. Died after a severe haemorrhage, 6/7/16.

P.-M. Fragment of shell-casing in right upper lobe. Right lung com-

pletely collapsed and covered with purulent lymph. Right heart dilated. Fatty change in liver and kidneys. Spleen large, soft, and pale.

Case 14. Wounded 13/11/16, admitted 19/11/16. Rifle-bullet wound perforating left chest. Air and blood were passing through the entrance wound over left clavicle. T. 101·5°; mucopurulent sputum. Much subcutaneous emphysema over whole of left chest. 20/11/16. Left chest explored in two places —thin brownish fluid withdrawn from one, and pus from the other. Resection of rib and drainage. Patient's condition did not improve after the operation, and he died 24/11/16.

P.-M. Collapse of left lung with laceration in track of bullet. Pleura coated with purulent lymph. Early broncho-pneumonia right lung. Predominant organism in fluid withdrawn by exploring syringe was a Gram-positive diplococcus.

Case 15. Wounded 2/7/16, admitted 9/7/16. Rifle-bullet wound perforating lower part of right chest. T. 100·2°. Fresh streaks of blood in sputum, signs of pneumo-haemothorax right side, pleurisy both sides. 12/7/16. Bile escaping from exit wound in back. 15/7/16. Explored pus and blood containing anaerobic organisms. 16/7/16. Liver explored and abscess drained. One rib found to be fractured. Patient continued to discharge large quantities of bile from the wound. His stools became clay-coloured. General condition rapidly became worse. Temperature fluctuated between 103·4° and 99·4°. Died 19/7/16.

P.-M. 26/7/16. Pleurisy both lungs. Right lobe of liver extensively lacerated. Gall-bladder empty. Right kidney wounded. All organs in advanced state of decomposition and with characteristic appearance of anaerobic infection.

Case 77. Wounded 10/7/16, admitted 13/7/16. Shrapnel wound perforating right chest. T. 98°. Signs of large right haemothorax. Heart pushed over to left. 15/7/16. Explored, blood withdrawn from which no growth was obtained. T. 101°. General condition bad. 16/7/16. Right side much swollen and oedematous. Opened and drained. Patient died following night.

P.-M. 17/7/16. Ninth rib fractured in two places and parietal pleura torn. Two pints bloody fluid right chest. Lower lobe bruised and collapsed. Left chest generalized, pleurisy, whole lung adherent. Some fatty changes in liver and kidney, spleen slightly enlarged, and soft anaerobic infection.

Case 78. Wounded 14/7/16, admitted 17/7/16, with a wound over cartilages of sixth and seventh ribs near sternum, left side. Projectile unknown. Praecordial dullness enlarged to right. Signs of large left haemothorax and right-sided pleurisy. Dyspnoea, cyanosis. T. 99·8°. 22/7/16. Aspirated 22 oz. 23/7/16. No relief of symptoms. Temperature fluctuating between 98° and 101·5°. Attempt made to puncture pericardium, about 4 oz. of blood withdrawn. Patient became worse and died in the evening.

P.-M. 24/7/16. Fracture tip of sixth left rib. Septic pericarditis. Left pleura wounded (haemothorax). Diaphragm pierced and liver wounded. Right sero-fibrinous pleurisy. The exploring needle had passed into right ventricle, but there was no evidence of escape of blood into pericardium.

Case 125. Wounded 17/11/16, admitted 19/11/16, with shrapnel wounds on lower part right chest. Signs of small haemothorax on right side, heart normal. Foreign body localized below diaphragm by X-ray. T. 102·4°. 22/11/16. Vomiting, deep jaundice, yellow discharge from wound. Temperature had ranged from 100° to 104°. Patient died early next morning.

P.-M. 23/11/16. Right lung early pleurisy and some bloody fluid in pleura. Liver much lacerated, foreign body in right lobe. Much haemorrhage into peritoneum. All organs in advanced state of decomposition owing to anaerobic infection.

Case 156. Wounded 21/8/16, admitted 27/8/16. Shell wound over fourth to fifth rib cartilages close to right border of sternum, with fracture of lower right costal cartilages. Wounds of face, arms, and left thigh. Twenty-four hours after admission patient became delirious and temperature rose. The various wounds were opened up and drained, but he became worse and died, 3/9/16.

P.-M. 4/9/16. Purulent meningitis (? from infection by wound in left cheek). Pus over pericardium and necrosis tracking down in sheath of right rectus abdominis muscle. Gas gangrene of all organs.

Case 157. Wounded 6/6/16, admitted 8/6/16, with wounds over left scapula. History of blood passed per rectum on day after injury. Slight fresh haemoptysis. General condition very fair. 11/6/16. Occasional vomiting. Temperature raised. A tarry motion. 14/6/16. No abdominal symptoms, pain in left side, no further vomiting, general condition improved. 16/6/16. Vomiting returned; much haemorrhage from rectum. Died.

P.-M. same day. No haemorrhage or pleurisy, slight wound of edge of left lung. Diaphragm perforated. Wound of third part of duodenum, which was firmly adherent to colon; no general peritonitis. Copious bleeding into bowel and peritoneum.

Case 158. Wounded 20/7/16, admitted 22/7/16, with extensive wounds superior maxilla, and superficial wound right elbow-joint caused by shrapnel; wound of lung over second intercostal space right side, in nipple line. Foreign body located in lung by X-rays. 31/7/16. Much foul discharge mixed with air from chest wound. No physical signs in the lung except rhonchi. 6/8/16. Opening in chest enlarged and drained. No foreign body felt. The patient got worse and died 10/8/16.

P.-M. 11/8/16. Other wounds clean. Lower part of right upper lobe and upper part right middle lobe lacerated and necrotic. Partial collapse and broncho-pneumonia of lower lobe. Small patches of purulent pleurisy. Foreign body outside pleura near angle of fifth rib, which was fractured. Fatty changes in liver and kidneys, spleen enlarged and congested.

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OBSERVATIONS UPON THE CALCIUM CONTENT OF THE BLOOD IN INFANTILE TETANY AND UPON THE EFFECT OF TREATMENT BY CALCIUM

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Introduction.

For more than a hundred years there have been in the literature satisfactory descriptions of infantile tetany. J. Clarke (1815) (1), Cheyne (1819) (2), and Marshall Hall (1841) (3), and doubtless others reported the clinical histories of patients with convulsions, spasm of the glottis, and contractures of the hands and feet with sufficient detail to allow us to recognize that they were dealing with tetany. Moreover, they realized themselves that these symptoms were frequently found together and that the presence of one was presumptive evidence of the presence of others. Yet for a long time these excellent observations were overlooked, and attention was directed to the search for the cause of single symptoms rather than for the explanation of the disease as a whole.

After a lapse of many years Cheadle (4) redirected attention to the fact that all the symptoms that had been the subject of individual study were after all manifestations of a common fundamental condition that varied in so far as it allowed various combinations of these symptoms to find expression. He insisted also that the tetany of infants and the tetany of adults were essentially similar. One of his statements might, even now, stand as representative of the most modern opinion: 'But in the vast majority of cases there exists as a predisposing cause a special constitutional state, in which the nervous system is in an extreme state of hyperexcitability or motility—a state of "erethism" as it is called, and in this state slight causes of irritation which would be innocuous in a condition of stability set up the muscular motor spasm of laryngismus, tetany, or general convulsions.'

The Diagnostic Criteria of Tetany.

Before this statement of Cheadle, three diagnostic measures or signs had been devised for the recognition of tetany during or in the intervals between its

clinical manifestations. These were Trousseau's phenomenon, Chvostek's or the facial phenomenon, and Erb's sign, or hyperexcitability to the galvanic current. But for some years it was only the first of these that was noticed to be applicable to the tetany of children. Trousseau observed the assumption of the typical 'main d'accoucheur' position by a young child when the blood-vessels of the arm were constricted. When the attempt was made in the early nineties of the last century to utilize these signs for the diagnosis of infantile tetany much opposition was encountered, and it was vigorously asserted that the tetany of infants and the tetany of adults were two separate conditions bearing no relationship, and that therefore the criteria for the diagnosis of the one were inapplicable for the diagnosis of the other. It is unnecessary to argue here as to the unity or duality of the conditions—it is enough that these signs are the final criteria upon which many a diagnosis of tetany is based. Moreover, during the period of quiescence of the symptoms or during the 'latent' period before the development of symptoms, it is by them and by them alone that we can recognize the presence of tetany.[1]

The valuation to be put upon these symptoms has undergone some change and there is not yet entire agreement as to their specificity. It is generally agreed that Trousseau's sign is indicative of tetany. It occurs so far as known in no other condition. It is, however, frequently absent with frank, outspoken tetany. Its absence therefore indicates nothing. Regarding Chvostek's sign there is much difference of opinion. It is often found with older children when there is to be obtained no history of tetany and no symptom even suggesting it. It is far more common in older children than in infants. Thiemich (5) and Herbst (6) maintain that it invariably points to tetany. In the opinion of the majority this is too sweeping a statement, and we believe it to be so for older children, but we have never found the facial phenomenon in children under two years of age unless other unmistakable evidences of tetany have also been present. In children over three years it is not uncommonly found, especially in its milder grades. We therefore do not attach great importance to Chvostek's sign after the second year unless it is especially marked.

Hyperexcitability to the galvanic current in adult tetany was first mentioned by Erb in 1874 (7). He observed a uniform increase in the reactions but made no quantitative determinations. Escherich and his assistants were the first regularly to apply electrical reactions to the diagnosis of tetany in infants. Though passing reference should be made to the fact that Stewart had observed, in 1889, that a galvanic hyperexcitability was present in infantile tetany, regular application of electrical reactions to the diagnosis of tetany first began to be made after 1890, following the observations of Escherich (8), Ganghofer (9), Burckhardt (10), and others. A satisfactory basis for the utilization of this method of diagnosis was laid by the work of Thiemich (11) and Mann (12) in 1899. They called attention to the fact that the most definite information is to

[1] We consider as tetany or 'latent' tetany the conditions variously spoken of as 'spasmophilia', 'the spasmophilic diathesis', &c.

be obtained from the amount of current necessary to cause a cathodal opening contraction. In young, normal infants this contraction is not obtained with a current of less than 5 milliampères, whereas in the presence of tetany a contraction with a current less than this is regularly obtained. Cathodal closure tetanus, which renders determination of the opening contraction impossible with a current less than 5 milliampères, has the same significance.[2] This diagnostic criterion has received general acceptance.

Von Pirquet has called attention to the frequency of an anodal hyperexcitability in tetany as shown by an anodal opening contraction with a current less than 5 milliampères and by a reversal of the anodal contractions, that is, an anodal opening contraction occurring with a current less than is sufficient to cause an anodal closing contraction.[3] Von Pirquet (13) believes that this anodal hyperexcitability, in the absence of other symptoms, indicates a latent form of tetany. Holmes (14) has recently made a very comprehensive study of the electrical reactions, and has shown that many apparently normal children over six months of age show a reversal of the anodal reactions and frequently have an anodal opening contraction with a current less than 5 milliampères. As age increases this is found more and more often, and is present in the majority of children of five years or more. He therefore believes that the anodal hyperexcitability can only be considered indicative of tetany in the first six months of life, when the nerves are most refractory to the passage of the current. Tetany in older children is to be diagnosed by means of anodal reactions only when the reversal is present and when the contractions occur with a very weak current, i. e. less than 2 milliampères.

Theories as to the Causation of Tetany.

The diagnosis of tetany at the present day from clinical symptoms and by means of the accessory diagnostic signs may be made with sufficient accuracy; it is another matter to determine what it is that brings about this strange hyperexcitability of the nervous system to insults and stimuli of all kinds. There have been many hypotheses suggested. None have been as yet entirely convincing. It has been vigorously insisted by Kassowitz and his adherents that tetany is only a symptom of rickets. It is quite true that rickets is usually to be found associated with tetany, and that tetany is most common during the winter and spring months, when active rickets is also most frequently seen. The chief objections to this hypothesis are that tetany is found at times when no rickets is discoverable and that very many children with the most extreme evidences of rickets never manifest any evidences of tetany. If tetany were

[2] Thiemich and Mann used the median nerve. The same statement also applies if other nerves are used. It is our custom to use the peroneal nerve.

[3] With the majority of healthy infants an anodal closing contraction takes place with a current less than is required to cause an anodal opening contraction.

merely a symptom of rickets, there should be a greater parallelism between the severity of the two.

Tetany has been referred to an improper diet, to an absence of breast milk, or to an excessive quantity of cow's milk. Finkelstein believed the offending substance to be contained in the whey of cow's milk. That no food can be held solely responsible is shown by the fact that tetany may be seen after almost any form of diet. Children may manifest it after receiving cow's milk in too large a quantity or when the milk intake has been carefully regulated. They may show tetany when receiving a preponderately carbohydrate diet, or they may develop tetany (and this is especially frequent with the coloured) when receiving the breast exclusively. Infants may begin to improve at once when, after a too exclusive carbohydrate diet, cow's milk in moderate amount is added. The same may be true when carbohydrate is added to feedings of milk alone. While breast-feeding usually brings about a cessation of the manifestations of tetany, it does so only slowly, and the continuation of breast-feeding to an infant already suffering from tetany, even if it be breast-feeding by another woman, does not improve matters. No one can deny that tetany is far more common in the artificially fed than it is in the breast fed, but it is difficult to go farther and say why this is so or what substance it is that by its presence or absence is responsible for the production of tetany.

Tetany has also been referred to the absence of an essential substance or 'vitamine' in the diet. In support of this view may be mentioned the preponderance of tetany among the artificially fed and the considerable improvement brought about by cod-liver oil.[4] Against this view is the fact that many cases of tetany are to be seen when the diet of the infants has been composed wholly or in part of cow's milk, which has not been heated so as to destroy the 'vitamines'. This view is in accordance with the prevalent opinion regarding many of the obscure nutritional disturbances, but it lacks any very definite proof.

Noel Paton (15) and his collaborator have recently made an extensive study of tetany in animals and in human beings. They believe that the tetany of animals deprived of their parathyroid glands and the idiopathic tetany of infants are similar as regards their characters and metabolism, and that both are due to some error in metabolism whereby an intoxication by guanidin and methylguanidin takes place. Until the chemical studies upon which these conclusions are based can be repeated and confirmed it would be premature to venture a definite opinion regarding them. There are certain facts, however, that merit consideration. In the first place, enough studies have been made to show that parathyroid lesions in infantile tetany are the exception and not the rule, unless we assume that fatal tetany may result from purely functional disease of the parathyroids, no lesion remaining to give evidence of this fatal perversion of function. It should also be stated that parathyroid lesions as

[4] It is, however, asserted by several authors that no better results are obtained from cod-liver oil than from any other oil, unless phosphorus is also given.

severe as have been found after tetany may occur in patients who, during life, have shown absolutely no evidences of tetany, electrical or otherwise. The studies of Yanase (16) from Escherich's clinic, that led Escherich to place so much emphasis upon lesions of the parathyroids as the cause of tetany, have not been sufficiently confirmed. Another possible ground for criticism of Paton's conclusions is found in the small number of observations upon children and in the unsatisfactory ages of those children used for control. In his tables there is no mention of ages either among those free from or those suffering from idiopathic tetany. Most of the control patients were suffering from valvular disease or chorea, diseases which do not attack children of the tetany age. Finally, granting that the analytical method used by Paton determines guanidin and methylguanidin alone, no proof has been brought forward that the substances have accumulated in the blood of children. The blood of parathyroidectomized dogs was examined, but not that of children. Confirmation of these results and more extensive observations upon infants are required.

We have briefly mentioned above some objections to the view that parathyroid disease is the cause of infantile tetany. That there are many points of similarity between the tetany of parathyroidectomized dogs and human tetany is true. The symptoms are much alike as are also the electrical reactions. The changes that MacCallum and Voegtlin (17) found in the calcium of the blood are, as will be seen later, strikingly like those that we have found in the tetany of infants. But the experiments of Binger (18), to which allusion will shortly be made, show that typical tetany may be produced in dogs when the parathyroids are left entirely undisturbed. The burden of proof rests upon those who maintain the unity of the two conditions, and the proof is not yet complete.

The Rôle of Calcium in the Pathogenesis of Tetany.

More attention has probably been paid to calcium as a factor in the production of infantile tetany than to any other chemical substance. The close connexion between rickets and tetany, in the former of which there is a known error of calcium metabolism, has been sufficient to suggest to many a somewhat similar disturbance of calcium metabolism in tetany.

A great stimulus to the study of the relation of calcium to tetany was given by the observation of Sabbatani (19) and other Italian investigators, that a solution of calcium applied to the brain diminished its irritability to electrical stimulation, but substances that caused a precipitation of calcium, such as oxalates or citrates, brought about an increased irritability. Quest (20), Cohn (21), and Aschenheim (22) examined the brains of children dying from tetany and from other causes. Although there was a considerable diminution of the calcium in some of the tetany cases, there was little regularity in the results,

and the observations were so few that no definite conclusion is to be drawn from these studies.

Gregor (23) made observations upon two children that seemed to prove that woman's milk diminished and cow's milk increased the electrical excitability of infants. Finkelstein thereupon emphasized the importance of cow's milk in producing tetany and concluded that as casein and fat did not increase the symptoms, it was some constituent of the whey that was responsible. Stoeltzner (24) then put forward the hypothesis that tetany was the result of poisoning by calcium, caused by an accumulation of calcium in the blood, in consequence of a clogging of the usual paths of excretion. He supported his hypothesis by some electrical reactions made after giving calcium to infants and by some remarkable physiological considerations. Faulty as was Stoeltzner's reasoning, his paper nevertheless stimulated a number of men to undertake somewhat similar observations in an effort to disprove his views. Bogen (25), Risel (26), Rosenstern (27), von Pirquet (13), and Zybell (28) gave calcium in various forms and in varying doses by mouth. They determined its action by the effect upon the electrical reactions. Not only did they find no exciting influence, but in the majority of instances quite the opposite was found. All came to the conclusion that there was no reason to believe in the truth of Stoeltzner's hypothesis.

The favourable therapeutic influence of calcium upon tetany which will subsequently be discussed, gives weight to the view that a deficiency of calcium may play a part in the production of tetany.

Studies upon the calcium metabolism of infants with tetany, have been made by von Cybulski (29) and Schabad (30). The former found a very slight calcium retention during active tetany and a greatly increased retention during convalescence. Schabad's results were similar. He came to the conclusion that there was absolutely no difference to be determined between the metabolism of uncomplicated rickets and of rickets complicated by tetany, and stated that the information to be desired could be obtained only by analyses of the blood. He, however, made none. It is not to be expected that with the ordinary metabolism methods a differentiation between rickets and tetany could be made. A loss of an excessive amount of calcium does not necessarily mean that the calcium in the blood is low. Following poisoning with acids there is a marked excretion of calcium, and the same occurs in diabetes, yet Allers and Bondi (31) found a very greatly increased calcium content of the blood after poisoning rabbits with hydrochloric acid.

The attempt has been made by Neurath (32), Cattaneo (33), and Longo (34) to determine the calcium in the blood. Neurath used Wright's method, which depends upon the amount of oxalate that must be added to prevent the coagulation of blood. It is supposed to show differences in the amount of free calcium ions. It gives relative but not absolute figures. Neurath examined the blood of fifteen infants with various manifestations of tetany of more or less severity. He found in general a reduction of the calcium. No determinations were made upon patients with rickets alone.

Cattaneo and Longo have made gravimetric determinations of the calcium in the blood of a few normal children and of a few with tetany. Cattaneo does not give his method nor the ages of the children, nor does he mention the amount of blood used in the determinations. He found the following percentages of CaO in the blood:

I.	Healthy	0·6832
II.	Rachitic	0·3060
III.	Cured of tetany	0·3156
IV.	Tetany	0·0240
V.	Tetany	0·0219
VI.	'Girospasm'	0·0114
VII.	Eclampsia	0·0877

Without knowing the methods of analysis, one cannot tell how much importance should be attached to these figures. That scepticism regarding them is justifiable is shown by the enormous quantity of Ca found in the blood of the normal child, a far greater amount than has ever been determined before or since, and by the great difference between this amount and that found in tetany. The difference in one instance is 6,000 per cent.

Longo determined gravimetrically the calcium in the blood of eight children, using 25 c.c. of blood. The determinations were apparently not made in duplicate. His figures for the percentage of CaO in the blood were as follows:

I.	Tetany, severe, 22 months	0·01718
II.	Tetany, latent, 24 months	0·01662
III.	Tetany, severe, fatal	0·0252
IV.	Normal, 15 months	0·02116
V.	Normal, 36 months	0·01750
VI.	Normal, 30 months	0·01406
VII.	Normal, 17 months	0·02078
VIII.	Normal, 24 months	0·01949

Longo stated that the great differences between his figures and Cattaneo's were perhaps referable to the fact that Cattaneo used younger children, a supposition unjustified in the light of our determinations. Longo concluded, 'It is impossible to establish any relationship between the calcium contained in the blood and any spasmophilic manifestation'.

The studies upon parathyroid tetany in animals are of great interest on account of the influence of parathyroidectomy upon the calcium of the blood. MacCallum and Voegtlin (17) and MacCallum and Vogel (35) have shown that after parathyroidectomy tetany appeared when the calcium of the blood was diminished about one-half, and that the symptoms of tetany could be promptly, though only temporarily, relieved by the intravenous administration of calcium salts.

Over a year ago we showed (36) that in the acidosis of nephritis there is a

great accumulation of inorganic phosphates in the blood serum, and that when the phosphates are increased there is a reduction of the calcium, sometimes to a very low point. On the basis of these findings Binger (18) has recently published most interesting observations upon the effect of the intravenous administration of phosphate solutions to dogs. When sodium phosphate in sufficient quantity and at the right reaction is injected, definite tetany results with a marked decrease in the calcium of the serum. If the solution injected has a hydrogen ion concentration greater than 10^{-6} no tetany results even though the calcium drop occurs.

The Calcium of the Blood under Normal Conditions.

We have studied the relationship of calcium and infantile tetany during the last two and a half years. It is apparent that merely from the determination of the intake and excretion of calcium little can be learned. It is of prime importance to determine the quantity of calcium circulating in the blood. With the usual methods of analysis this has been impossible unless 50 or 100 c.c. were withdrawn, with double the amount if duplicate determinations were made, an impossible procedure with living infants. It was therefore necessary to develop an accurate method that would allow duplicate determinations to be made with a small amount of blood. This we have done (37). The method is sufficiently exact to determine the calcium in 2 c.c. of serum with an error of not more than 5 per cent. The method is time-consuming and requires a considerable degree of experience in the various manipulations and in the final readings, but others beside ourselves have used it with as much success as have we. The method depends upon the ability of the oxalate ion to decolorize a solution of ferric thiocyanate. The calcium of the serum is isolated as the oxalate; this is dissolved in dilute hydrochloric acid and is determined by comparison with the decolorization produced by a known amount of oxalic acid. We have used blood serum in our determinations, for there is practically no calcium contained in the corpuscles. This obviates the necessity of removing the iron or of considering the number and volume of the corpuscles. The results upon serum under normal conditions are almost exactly twice as great as upon whole blood, since approximately fifty per cent. of the volume of the latter is corpuscles.

We determined first the calcium in the serum of normal persons. The amounts found are given in Table I.

TABLE I. *Normal.*

Milligrams of Calcium per 100 c.c. of Serum.

Placental	11·3
Placental	11·0
Placental	10·8
Placental	10·7
6 weeks	11·0
3 months	10·0
3 months	11·0
5 months	10·8
15 months	11·0
Adult	11·2
Adult	11·3
Adult	9·2
Adult	10·0
Adult	10·3
Adult	11·0
Adult	9·8

It will be seen from the table that the quantity of calcium in placental serum and in the serum of normal patients is singularly constant. In almost all instances, no matter what the age, and in all instances with infants it was above 10·0 mg. and it is seldom more than 11 mg.

The Calcium of the Blood in Rickets.

On account of the frequent association of rickets with tetany it was necessary to determine if any changes in the calcium of the serum result from rickets alone. We have therefore studied a considerable number of cases of rickets. It is well recognized from pathological studies, particularly those of Schmorl (38), that rickets is often not a continuous process. There occur periods of remission and exacerbation, sometimes several in succession. These are difficult to determine from clinical symptoms alone, especially if one relies upon alterations in the bones. In these periods of remission it has been shown by metabolism studies that calcium is retained; in the periods of exacerbation there is either an insufficient retention or an actual loss of calcium. In order to obtain, if possible, blood from patients with active rickets we have made our studies only in the winter and spring months, when it is known that rickets is most prevalent and apt to be active. We have also studied a series of infants with early manifestations of the disease. The presence of a considerable proportion of coloured patients in our out-patient department makes this possible. These coloured infants, even when breast fed, frequently manifest severe evidences of rickets after the fourth month.

The eight four months old infants that we have studied showed craniotabes, sweating about the head, and enlarged spleens, which were not due to syphilis. One patient only had a positive Wassermann reaction. It is, in our opinion, not likely that, with marked symptoms at what must be a short time

after the onset of the disease, these cases would be in a condition of remission. We have therefore called them 'active'. At a later period than this it is difficult to speak with such assurance. With older patients we have called the symptoms 'mild', 'moderate', or 'marked' according to the changes in the skull and epiphyses, the delaying of dentition, and the alterations in the density of the bones and at the epiphyses as shown by the radiograph. The one case marked 'very severe' was in a twenty-three months old child who died as the result of thoracic rickets and atelectasis. There were multiple fractures. The following are the results obtained in 21 cases:

TABLE II. *Rickets.*

Milligrams of Calcium per 100 c.c. of Serum.

No.	Child.	Race.	Age.	Type of Rickets.	Calcium.
1	A. T.	Coloured	4 months	Active	10·9
2	R. W.	Coloured	4 months	Active	9·0
3	C. J.	Coloured	4 months	Active	10·5
4	L. D.	Coloured	4 months	Active	7·9
5	D. S.	Coloured	4 months	Active	9·0
6	G. D.	Coloured	4 months	Active	8·0
7	E. F.	Coloured	4 months	Active	9·0
8	H. L.	Coloured	4 months	Active	8·3
9	E. B.	Coloured	4 months	Active	9·3
10	B. S.	Coloured	6 months	Mild	10·9
11	M. S.	White	6 months	Mild	10·7
12	C. F.	White	6½ months	Moderate	8·6 9·0
13	M. S.	White	8 months	Mild	10·9
14	T. L.	White	8 months	Moderate	9·0
15	L. W.	White	8 months	Marked	10·5
16	F. F.	White	9 months	Marked	9·0
17	E. V.	White	10 months	Mild	8·0
18	R. Q.	Coloured	12 months	Mild	9·8
19	R. Q.	Coloured	14 months	Mild	8·8
20	J. M.	White	20 months	Marked	10·0
21	S. J.	Coloured	23 months	Very severe	9·3
				Average . .	9·4

An examination of the figures in Table II shows that in more than a third of the cases the figures fall within the normal limits, and this even when the disease was presumably active (in the fourth and sixth months). In nine cases there was a slight reduction, so that there were found between 9 and 10 mg. of calcium per 100 c.c. In five cases the calcium content was from 7·9 to 8·8 mg. The lowest amount that we have found in apparently uncomplicated rickets was 7·9 mg. We may say, then, that with rickets there is no great reduction in the calcium, that while the calcium may be reduced as much as 2 mg. per 100 c.c. (20 per cent.) the considerable majority show a reduction of 1 mg.

(10 per cent.) or less, and that with cases of apparently active rickets there may be no reduction whatever. The calcium reduction does not seem to be obligative. Attention should be called here to a question which subsequently will be more fully discussed. A number of the children, the calcium content of whose serum was below 10 mg., were studied electrically. There were eight of these, and of them seven demonstrated an anodal hyperexcitability. Of four whose calcium content was normal only one showed an anodal hyperexcitability. The possibility of a very early tetany should be kept in mind as an explanation for the low calcium. But even then the reduction is not great and cannot be compared in any way to that occurring with cases of active tetany, as will shortly appear.

Calcium of the Blood in Tetany.

In choosing cases of tetany for study we have taken those regarding the diagnosis of which there could be no doubt whatever. All of the children had had or were having convulsions, with all there was a cathodal opening contraction with a current less than 5 milliampères, a number had spasm of the glottis, and with many Trousseau's sign or a marked facial phenomenon, or both, were demonstrated.

The following are the histories, in abstract, of the patients we have studied:

Case I. Mary G. 10,464. White. 8 months.

Nursed two months, then received half milk and half water. Much vomiting and constipation. March 16, 1916, had convulsions and from time to time since then carpopedal spasm.

Admitted to the hospital March 27, with otitis media and bronchitis. Child poorly nourished, slightly rachitic. Weight 12 lb. 11 oz. Chvostek, 0.

March 27. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·8	2·0	0·8	4·5

Calcium in serum, 6·0 mg. per 100 c.c.

Child had fever for twelve days. No more convulsions. Improved rapidly thereafter.

April 22. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	1·1	2·0	5·0	>5

Calcium in serum, 10 mg. per 100 c.c.

Case II. Anna H. 13,936. Coloured. 5 months.

Breast fed for four months, then received supplementary feedings of condensed milk. Since a month of age, child has had snuffles and for a week eruption on face and scalp. A few days before admission had 'spells' in which she stiffened out and clenched her fists. She had a crowing inspiration. The convulsions were very frequent, occurring every half-hour to an hour. Admitted to the hospital on the 19th of April. A poorly nourished infant, weighing 9 lb. 8 oz. Evidences of syphilis. Wassermann, + + + +. Signs of consolidation at right base, posteriorly. Temperature irregular, between 99° and 104° F. Chvostek, +. Trousseau, 0.

April 19. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·4	3·0	1·0	4·5

Calcium in serum, 5·7 mg. per 100 c.c.

Calcium chloride given, grm. 0·5 q. 4 h. No more convulsions. May 7, calcium chloride discontinued.

	C.C.	A.C.	A.O.	C.O.
May 16. Electrical Reactions:	1·8	>5	4·5	>5

Calcium in serum, 7·5 mg. per 100 c.c.

Case III. Sadie J. 14,069. Coloured. 9 months.

Breast fed, whenever infant cried, for three months; thereafter rice, barley-water, and cereals in addition. History very unsatisfactory.

April 23. There was a general muscular spasm and these convulsions have been repeated since.

April 30. Admitted to the hospital. A poorly nourished coloured child, weighing 12 lb. Marked evidences of rickets. Chvostek, +. Trousseau, 0. Slight carpopedal spasm.

	C.C.	A.C.	A.O.	C.O.
Electrical Reactions:	0·8	1·8	1·1	2·0

Calcium in serum, 5·5 mg. per 100 c.c.

Calcium chloride given, grm. 0·5 q. 4 h.

	C.C.	A.C.	A.O.	C.O.
May 4. Electrical Reactions:	1·2	>5	3·8	>5
May 18. Electrical Reactions:	2·0	>5·0	5·0	>5
May 22. Electrical Reactions:	2·2	>5·0	5·0	>5

Calcium in serum, 8·5 mg. per 100 c.c.

Magnesium in serum, 2·7 mg. per 100 c.c.

There were no convulsions after giving the calcium chloride. On May 22 this was stopped.

	C.C.	A.C.	A.O.	C.O.
May 28. Electrical Reactions:	2·0	>5	4·0	>5

Calcium in serum, 8·0 mg. per 100 c.c.

Magnesium in serum, 3·0 mg. per 100 c.c.

Case IV. Edward N. 13,992. White. 13 months.

Breast fed alone for thirteen months. Then received orange juice, farina, bread and butter, and tea. Well up to present illness. On February 2 child had a convulsion without any apparent cause. The first week in March had two or three convulsions and thereafter an increasing number, often as many as four or five a day. Mother had noticed carpopedal spasm and inspiratory crow.

Immediately after admission to the hospital on the 23rd of April child had another convulsion. He was stout and well-nourished, with slight evidences of rickets. Chvostek, +. Trousseau, +.

	C.C.	A.C.	A.O.	C.O.
April 23. Electrical Reactions:	0·5	3·2	1·6	3·6

Calcium in serum, 5·0 mg. per 100 c.c.

Calcium chloride given, grm. 0·5 q. 4 h.

	C.C.	A.C.	A.O.	C.O.
April 27. Electrical Reactions:	2·0	>5	3·0	>5

Calcium in serum, 7·0 mg. per 100 c.c.

No more convulsions after calcium chloride medication. Seen on the 17th of May. No more convulsions and seemed entirely well.

Case V. John P. 9,022. 5 months. White.

Artificially fed from birth. On the 13th of January developed convulsions. Admitted to the hospital on that day and had a series of convulsions immediately

after admission. These were controlled with difficulty by magnesium sulphate subcutaneously and by chloroform and chloral. A poorly nourished child, weighing 10 lb. 12 oz.

January 13. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·8	2·4	1·6	2·0
January 15. Electrical Reactions:	0·3	0·4	1·1	1·5

Calcium in the serum, 5·0 mg. per 100 c.c.

The convulsions continued unabated, there was much difficulty with inspiration, and the child died of exhaustion on January 26.

Case VI. William P. 13,111. Coloured. 3 years 4 months.

Had been breast fed for a year and thereafter had received a general diet. On January 18 became suddenly ill with fever and with pain in the extremities. He was admitted to the hospital on January 19, with a temperature of 104° F., and with marked evidences of bronchitis. He had had a convulsion before admission to the hospital. Chvostek, +.

January 18. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·3	2·5	0·7	2·0

Calcium in serum, 5·8 mg. per 100 c.c.

The temperature fell to normal within two days after admission. He improved very rapidly and went home on the 25th of January.

Electrical Reactions on discharge:	C.C.	A.C.	A.O.	C.O.
	1·5	3·0	2·8	>5

Case VII. George S. 13,809. White. 5 months.

Child never nursed. Mellin's food and milk since birth. Two days before admission to hospital began to have convulsions, and these were repeated at irregular intervals. Admitted to the hospital April 3. A moderately nourished child with slight evidences of rickets. Carpopedal spasm slight. Trousseau, +.

April 3. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	1·0	3·0	1·0	3·4

Calcium in serum, 3·5 mg. per 100 c.c.

Magnesium in serum, 2·7 mg. per 100 c.c.

April 5. Calcium chloride given, grm. 1·0 q. 4 h.

April 15. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	2·2	>5	>5	>5

Calcium in serum, 7·5 mg. per 100 c.c.

Magnesium in serum, 2·2 mg. per 100 c.c.

The evidences of tetany disappeared after taking calcium, but the temperature of the child, which was elevated on admission, remained continuously high and he developed signs of consolidation at both bases. He died on the 20th of April without any recurrence of his symptoms of tetany.

Case VIII. Margaret S. 13,122. Coloured. 6 months.

Breast fed for one month and thereafter received additional feedings of milk and water with bread. Four days before the child was admitted to the hospital the mother noticed that her milk stopped and that her hands were contracted. For two days she had had some difficulty with respiration. The day before admission the feet became stiff. She was admitted on the 20th of January, a well-nourished child, weighing 13 lb. Slight evidences of rickets. Hands and feet in typical position of tetany. Chvostek, +. Trousseau, +.

January 20. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·1	0·8	0·5	1·0

Calcium in serum, 5·0 mg. per 100 c.c.

Feedings: Breast milk, five feedings, 4 oz. each. Received 6 c.c. of 16 per cent. solution of magnesium sulphate intramuscularly.

January 27. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·5	2·5	1·0	2·0
February 13. Electrical Reactions:	0·6	4·8	1·1	4·8

Calcium in the serum, 6·3 mg. per 100 c.c.

Discharged from hospital much improved.

March 9. Brought back to the dispensary. Carpopedal spasm had returned, also spasm of the glottis. Chvostek, +. Trousseau, +.

Calcium in the serum, 5·0 mg. per 100 c.c.

March 17. Carpopedal spasm increased. Admitted to the hospital. Spasm of the glottis marked.

Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·2	1·6	0·5	1·4

Calcium in the serum, 4·5 mg. per 100 c.c.

Magnesium in the serum, 1·6 mg. per 100 c.c.

Calcium lactate ordered, grm. 1·0 t. i. d.

March 22. Trousseau, 0. Chvostek, +. Spasm of the glottis less marked.

Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·4	2·8	1·2	2·8

Calcium lactate stopped and calcium chloride ordered, 0·5 grm. every four hours.

March 23. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·8	>5	1·8	>5
March 29. Electrical Reactions:	1·4	>5	2·8	>5

Calcium in serum, 8·5 mg. per 100 c.c.

Magnesium in serum, 1·7 mg. per 100 c.c.

Discharged on March 31. Chvostek, +. Trousseau, 0. Still taking calcium. Two days later developed a high fever, the result of bronchitis (104° F.), and for a few hours had carpopedal spasm. Temperature fell within less than twenty-four hours and the carpopedal spasm entirely disappeared. No calcium studies made at this time.

Case IX. Irvin J. 9,269. Coloured. 18 months.

Nursed to date. Two days before admission to the hospital on February 20 the child had general convulsions. He was well nourished, weighing 16 lb. Moderate evidences of rickets. Marked carpopedal spasm. Chvostek, +. Trousseau, +.

February 20. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·4	0·5	0·6	0·9

Calcium in serum, 4·7 mg. per 100 c.c.

Inorganic phosphorus in serum, 3·0 mg. per 100 c.c.

February 21. Calcium chloride given, 0·5 grm. every four hours. Thereafter no more convulsions and rapid disappearance of carpopedal spasm and Trousseau's sign.

February 26. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	2·4	2·8	>5	>5

Calcium in serum, 8·45 mg. per 100 c.c.

Case X. Harry H. 13,858. Coloured. 6 months.

Breast fed for three months, afterwards received condensed milk and Mellin's food. A month before admission to the hospital had convulsions which occurred almost every hour for seventy-two hours. Seemed well thereafter until the day before admission to the hospital, when he had another convulsion.

Admitted to the hospital April 9. A well-nourished child, showing marked evidences of rickets. Chvostek, 0. Trousseau, 0.

April 9. Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	0·8	3·4	2·0	4·8

Calcium in serum, 5·8 mg. per 100 c.c.
Magnesium in serum, 3·0 mg. per 100 c.c.
Calcium chloride given, grm. 0·5 q. 4 h.

April 17. Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	2·0	>5	>5	>5

Calcium in serum, 7·5 mg. per 100 c.c.
Magnesium in serum, 2·2 mg. per 100 c.c.

April 20. Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	2·0	>5	4·0	>5

Calcium in serum, 9 mg. per 100 c.c.

Case XI. Thelma W. 9,801. White. 2½ years.

One of twins. Artificially fed from birth and a number of different mixtures of milk and proprietary foods had been tried. For the last half-year she had taken all the articles in the average adult diet. In the first six months of life she had spasmodic attacks in which she became cyanosed and dyspnoeic. Never had any convulsions at that time. About October 1, 1915, she became exceedingly nervous. She would start at the slightest sound and apparently become very much frightened. She then had convulsions; these had been repeated many times. She developed carpopedal spasm and had marked spasm of the glottis.

Admitted to the hospital on January 7, 1916. A moderately nourished child with marked rickets. Trousseau, +. Chvostek, +. Typical carpopedal spasm.

Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	0·1	0·8	0·5	<4

Calcium in serum, 6·0 mg. per 100 c.c.
After a few days in the hospital the child was taken home against advice.

Case XII. Edward S. 14,086. Coloured. 21 months.

Breast fed for six months, then received oatmeal, milk, potatoes, vegetables, &c. From the description by the mother, it appeared that he had had attacks of carpopedal spasm since he was five months of age. A month before admission he had convulsions lasting about three hours. He had inspiratory crow. Since then, when crying, he had had difficulty in getting his breath. He was seen in the dispensary May 8.

Calcium in serum, 6·5 mg. per 100 c.c.

Calcium chloride ordered, grm. 0·5 q. 4 h. May 17, he was brought to the hospital, having had two convulsions the night before. It was practically certain that the child had taken no calcium chloride as the mother said he would not take food with it in at all. Trousseau, +. Chvostek, +.

May 17. Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	0·2	1·0	1·0	2·4

Calcium in serum, 6·15 mg. per 100 c.c.
Magnesium in serum, 2·2 mg. per 100 c.c.
Calcium chloride ordered, grm. 1·0 q. 4 h.

May 22. Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	1·8	3·0	3·0	>5
May 28. Electrical Reactions:	1·6	2·6	2·2	>5

Calcium in the serum, 8·2 mg. per 100 c.c.
Magnesium in the serum, 2·3 mg. per 100 c.c.
May 29. Calcium chloride discontinued.
June 1. On this date the carpopedal spasm and the inspiratory crow, which had disappeared shortly after the administration of calcium on the 18th of May, returned. Chvostek, +. Trousseau, +.
Calcium in serum, 6·3 mg. per 100 c.c.

Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·8	2·0	1·2	2·5

Phosphorus in serum, 4·0 mg. per 100 c.c. *Calcium chloride ordered again. Symptoms again disappeared.*
June 11. Calcium in serum, 7·3 mg. per 100 c.c.
Magnesium in serum, 2·7 mg. per 100 c.c.

June 14. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	1·0	2·2	1·8	>5

Case XIII. Mamie F. 8,341. Coloured. 7 months.
Breast fed for two months, then received condensed milk for two weeks, and for the last 4½ months two-fifths milk with small amount of sugar every three hours.
On the day before admission had three convulsions accompanied by fever, the latter due to otitis. Admitted to the hospital January 24. There was some inspiratory stridor. Slight evidences of rickets. Weight, 9 lb. 12 oz. Chvostek, +. Trousseau, +.

Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·4	1·2	0·8	1·8

January 24. Calcium in serum, 6·3 mg. per 100 c.c.
January 26. Calcium in serum, 6·5 mg. per 100 c.c.

Case XIV. Francis A. 13,984. White. 7 months.
Never breast fed. Condensed milk for six weeks, since then Mellin's food and milk. Digestion good. On April 8 had a typical convulsion; April 16, one convulsion; April 19, two convulsions; April 21, six convulsions. Admitted to hospital on this date.
Well-nourished child; weight, 14 lb. 10 oz. No evidences of rickets.

April 21. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	0·4	2·0	1·2	4·0

Calcium in serum, 6·8 mg. per 100 c.c.
After collection of blood, calcium chloride given, grm. 0·5 q. 4 h. No more convulsions.

April 27. Electrical Reactions:	C.C.	A.C.	A.O.	C.O.
	1·8	>5	3·5	>5

Calcium in serum, 9·0 mg. per 100 c.c.
Discharged April 28.
Child seen again June 4. No more convulsions. Appeared perfectly normal.

Case XV. Sadie B. 8,978. White. 8 months.
Admitted to the hospital March 5. Had previously been in the hospital at the age of five weeks for nutritional disturbance. Breast milk had been given and the child had gained rapidly in weight. For several months before present admission had been taking milk and barley-water, equal parts with 5 per cent. sugar added. Had gained well in weight.

On March 2 child had difficulty in inspiration and there was an inspiratory crow. She had a convulsion on the morning of admission and a severe convulsion shortly after admission to the hospital. Trousseau, 0. Chvostek, 0.

	C. C.	A. C.	A. O.	C. O.
March 4. Electrical Reactions:	0·5	2·0	1·0	3·8

	C. C.	A. C.	A. O.	C. C. T.
March 7. Electrical Reactions:	0·5	1·5	1·0	3·0

Calcium in serum, 6·0 mg. per 100 c.c.

The convulsions diminished in intensity and in two days ceased.

March 17. Phosphorus and cod-liver oil given, 4 c.c. t. i. d.

	C. C.	A. C.	A. O.	C. O.
March 24. Electrical Reactions:	0·9	2·4	2·0	>5
April 22. Electrical Reactions:	1·4	3·0	4·2	>5

Calcium in serum, 11·0 mg. per 100 c.c.

Case XVI. Edward D. 10,018. White. 17 months.

Admitted to the hospital January 31. Large child at birth. Had a convulsion on the second day of life, but no more until he was seven months old, then a slight one, and two more at seven and a half months. He had been breast fed until one month before admission to the hospital and since that time had been taking broth, cereals, bread, &c. When fourteen months of age he began again to have convulsions and they continued once or twice a week. They came on very suddenly. Each lasted about five minutes, accompanied by cyanosis. Child a strong, vigorous infant of 24 lb. Four teeth. Slight evidences of cyanosis. Chvostek, +. Trousseau, 0.

	C. C.	A. C.	A. O.	C. C. T.
Electrical Reactions:	0·8	2·0	1·6	4·0

Calcium in serum, 7·3 mg. per 100 c.c.

Case XVII. Nellie F. 13,507. Coloured. 6 months.

Admitted to the hospital March 6. No other food but breast milk from birth. Never ill before. Four days before admission, hands and feet became stiff and on the day before admission she had marked inspiratory stridor and also a severe convulsion, lasting one hour.

Child a fat, well-nourished infant, weighing 17 lb. Distinct evidences of rickets. Hands and feet in position of carpopedal spasm. Trousseau, +. Chvostek, +.

	C. C.	A. C.	A. O.	C. C. T.
March 7. Electrical Reactions:	0·6	2·2	0·8	1·3

Calcium in serum, 5·0 mg. per 100 c.c.

March 10. Calcium chloride given, grm. 0·5 q. 4 h.

	C. C.	A. C.	A. O.	C. O.
March 12. Electrical Reactions:	3·6	4·8	>5	>5

Calcium in serum, 8·5 mg. per 100 c.c.

No more convulsions. Rapid disappearance of carpopedal spasm and laryngospasm.

Seen again June 13, 1917. No evidences of tetany since discharge from hospital.

Case XVIII. Virginia F. 14,469. Coloured. 5 months.

Seen in dispensary June 11. Lactated very irregularly and received in addition cow's milk, soup, bread, &c. On June 9 child had a general convulsion, lasting six minutes; June 10, another short convulsion. Slight evidences of rickets. Chvostek, +.

June 11. Electrical Reactions:

C. C.	A. C.	A. O.	C. O.
1·4	2·1	1·0	4·5

Calcium in serum, 4·6 mg. per 100 c.c.
Phosphorus in serum, 2·7 mg. per 100 c.c.
Magnesium in serum, 2·7 mg. per 100 c.c.
Calcium chloride ordered, grm. 0·5 q. 4 h. No more convulsions.
June 18. Seemed well in every way.
Electrical Reactions:

C. C.	A. C.	A. O.	C. O.
1·8	>5	>5	>5

Calcium in serum, 8·0 mg. per 100 c.c. Chvostek, 0.
Magnesium in serum, 2·7 mg. per 100 c.c.

Table III gives in tabular form the calcium in the serum, during active symptoms, with the eighteen cases of idiopathic tetany which we have studied. In all the C. O. C. was less than five milliampères.

TABLE III. ACTIVE TETANY.

Milligrams of Calcium per 100 c.c. of Serum.

Case 1	6·0	Case 10	5·8
Case 2	5·7	Case 11	6·0
Case 3	5·5	Case 12	6·5
Case 4	5·0		6·15
Case 5	5·0	Case 13	6·3
Case 6	5·8		6·5
Case 7	3·5	Case 14	6·8
Case 8	5·0	Case 15	6·0
	6·3	Case 16	7·3
	5·0	Case 17	5·0
	4·5	Case 18	4·6
Case 9	4·7	Average	5·6

It will be noticed that the calcium was very greatly reduced in all instances, and with one exception was 7·0 mg. or less per 100 c.c., a reduction, roughly, in the neighbourhood of 40 per cent. It will also be noticed that the calcium was, in all instances, less than we have ever found with rickets and so much lower that, with one or two exceptions, there could be no danger of confusing even the highest determinations with the lowest which we obtained in rickets. From the regularity of our findings it appears that convulsions may be expected when the calcium content of the serum becomes less than 7·0 mg. per 100 c.c., or, to put it in another way, when there are convulsions and other symptoms due to tetany, the calcium of the serum is 7·0 mg. or less per 100 c.c. The amount of calcium in the serum that we found in idiopathic tetany is strikingly close to that which was found by MacCallum and Vogel (35) in the serum of dogs after parathyroidectomy.[5] They determined the calcium in whole blood.

[5] MacCallum and Voegtlin (17) determined the calcium in whole blood by the permanganate method. It is probable that an error crept into their calculations as their results in the normal, as well as in the dogs with tetany, were twice what one would expect. With due allowance for this and for the fact that they used whole blood, it appears that their results would have closely approximated 5·3, 6·5, 5·6, 4·6, and 5·2 mg. of calcium per 100 c.c. of serum.

Considering the calcium of serum twice that in an equivalent amount of whole blood, their results may be reckoned as 3·1, 6·4, 4·5, and 7·8 mg. per 100 c.c.

The results obtained by Binger (18) are also strikingly similar. He found that dogs, after injection with a sodium phosphate solution of the proper hydrogen ion concentration, developed tetany when the calcium in the serum was 5·6, 6·1, 5·5, and 5·3 mg. respectively, and that tetany did not develop when the calcium of the serum was reduced by the same measures to 7·8, 7·7, and 7·7 mg. respectively. We have also found, in studying the serum of two dogs subjected to parathyroidectomy, that the symptoms of tetany developed when the calcium was reduced to about 7·0 mg. Thus, one dog, before operation, had 10·8 mg. of calcium per 100 c.c. of serum; after forty-eight hours, a short time before the onset of tetany, 7·3 mg. The second had, before operation, 10·0; after twenty-four hours, 8·9; and after six days and with the onset of tetany, 6·8 mg. per 100 c.c. of serum.

The Calcium of the Blood in Convulsive Disorders other than Tetany.

The constancy of diminution of the calcium of the serum in tetany affords some means of differentiating tetany from other convulsive disorders in infancy. We have studied other cases of convulsions, manifestly not due to tetany, and have found the following:

TABLE IV. *Cases of Convulsions not due to Tetany.*

			Electrical Reactions.				
Patient.	Age.	Diagnosis.	C. C.	A. C.	A. O.	C. O.	Mg. of Calcium per 100 c.c. of Serum.
S. S.	4 months	Mental deficiency	1·8	> 5	> 5		10·1
C. de F.	1 year	Petit mal	2·4	> 5	> 5	> 5	11·0
D. N.	2½ years	Epilepsy	1·0	4·2	3·0	> 5	10·2
J. B.	5 years	Epilepsy					8·9
R. G.	7 months	Convulsions of unexplained origin					9·6
M. S.	6 months	Convulsions of unexplained origin	1·8	4·6	3·6	> 5	10·7
H. B.	7 months	Convulsions of unexplained origin	1·0	> 5	3·8	> 5	9·2

In the light of these results is it possible to refer tetany to a diminution of calcium in the blood? Perhaps the strongest evidence, in addition to the great parallelism which we have found between the symptoms and the low calcium content of the serum, is obtained by Binger after the injection of orthophosphates. When the calcium was reduced to a figure closely corresponding to what we found with active tetany, the characteristic symptoms of tetany in the dog appeared, and this when the parathyroids were entirely untouched. The prompt improvement in infantile tetany after calcium medi-

cation, as will be shown, and the absence of symptoms when the calcium in the blood remains above 7·5 mg., are also strong evidence as to the part that calcium plays in the production and dissipation of symptoms.

It seems sufficiently plain that the diminution in the calcium of the serum is a constant phenomenon in infantile tetany. What is it that brings about this diminution? There is, as we have indicated in the preliminary discussion, not yet sufficient evidence to prove the dependence of infantile tetany upon organic or even functional disease of the parathyroids, but the many points of similarity between human tetany and that occurring in dogs after parathyroidectomy, together with the close agreement in the calcium determinations, justify an open mind in regard to their influence.

Phosphates in the Blood in Tetany.

We have sought other explanations for the calcium diminution. As has been mentioned, Binger produced tetany by the intravenous injection of orthophosphates, and we have already shown that in severe nephritis with acidosis the calcium of the serum was greatly diminished when the inorganic phosphorus of the serum was high. The question, therefore, arises: Is there an accumulation of inorganic phosphates of the serum in tetany sufficient to account for the reduction of the calcium? This question can be answered at once in the negative. We have determined the inorganic phosphorus, as the protocols show, in active tetany, the calcium being low, and have not found an amount of phosphorus in the serum significantly above the normal limits, which are from 1 to 3·5 mg. per 100 c.c. of serum. We have found in tetany 1·0, 3·0, 4·0, and 2·7 mg. in different cases. There is also evidence that points to the fact that the reduction of calcium alone is not sufficient to bring about the symptoms of tetany unless certain other conditions are satisfied. Thus, with nephritis, even though the calcium of the serum may be diminished to a point below that which is found in tetany (in one of our cases there were but 1·5 mg. of calcium per 100 c.c. of serum), no symptoms of tetany usually result. This absence of tetany with calcium deficiency alone has been abundantly shown by Binger's experiments, a certain reaction of the injected fluid being necessary to produce tetany even though the calcium of the serum is greatly reduced.

The Relation of Alkalies to Tetany.

Wilson, Stearns, and Thurlow (39) showed that in dogs, at certain stages of tetany induced by parathyroidectomy, there was an increased alkalinity of the blood, called by them 'alkalosis'. This disappeared after the onset of convulsions. We have made determinations of the hydrogen ion concentration of the serum of infants with tetany by the dialysis indicator method, but have not found an 'alkalosis'. That tetany may, however, at times result from an alteration in the reaction of the blood we have had opportunity to observe.

After the therapeutic administration of bicarbonate of soda for acidosis, it is not unusual to see the development of characteristic symptoms of tetany. Thus, we have seen typical carpopedal spasm when bicarbonate of soda has been injected intravenously for the acidosis of diarrhoea. The three following histories show well the influence of soda in the production of tetany:

George L. 10,100. White. 3 years.

Badly burned as the result of setting fire to clothing. Admitted to surgical service of hospital with hyperpnoea and acidosis. RpH of serum, 7·9 (40). Bicarbonate of soda, grm. 13·0, given by mouth in divided doses. The symptoms of acidosis disappeared and within twelve hours he developed marked carpopedal spasm, a positive Chvostek sign, and the electrical reactions of tetany:

C. C.	A. C.	A. O.	C. C. T.
0·8	2·2	1·6	4·0

Calcium in serum, 7·5 mg. per 100 c.c.

Soda discontinued. In two days the symptoms disappeared and in three days the electrical reactions were normal.

Angelina B. 13,212. White. 9 months.

Admitted to the hospital with high fever and with severe, watery diarrhoea. Stools green; seven or more a day for several days. Leucocytes, 23,800. Signs of consolidation over the right upper lobe. On account of the severe diarrhoea and the possibility of the development of acidosis, the child received sodium bicarbonate, grm. 0·7 every four hours. Within twenty-four hours she was noticed to be stiff, and to have carpopedal spasm. Chvostek, 0. Trousseau, +.

Electrical Reactions:	C. C.	A. C.	A. O.	C. C. T.
	0·2	1·0	0·6	1·4

Calcium in serum, 6·0 mg. per 100 c.c.

Phosphorus, 2·0 mg. per 100 c.c.

The soda was at once discontinued and calcium chloride was given, 1·0 grm. five times a day. Her symptoms promptly disappeared. Two days later there was no carpopedal spasm, no Trousseau sign, and the electrical reactions were:

C. C.	A. C.	A. O.	C. O.
2·5	>5	>5	>5

Calcium in serum, 10·0 mg. per 100 c.c.

Goldie K. 14,909. 4 years 9 months.

Seen first in the dispensary on July 14, with a normal temperature but with a large amount of pus in the urine. Urine strongly acid. Sodium bicarbonate ordered and she took in a week 32 grm. Urine remained acid until the morning of July 20, when it was examined and found to be amphoteric. That same evening she suddenly complained of pain in her hands and feet. She had no fever and was perfectly conscious. She was brought to the hospital with her hands and feet in a typical carpopedal spasm.

Electrical Reactions:	C. C.	A. C.	A. O.	C. C. T.
	1·5	4·0	1·5	3·0

Hydrogen ion concentration of the blood serum by the dialysis indicator method: pH, 7·6; RpH, 8·4 (40).

Calcium in serum, 7·25 mg. per 100 c.c.

Phosphorus, 1·1 mg. per 100 c.c.

Soda at once discontinued and calcium chloride ordered, grm. 1·0 q. 4 h.

July 21. At 10 o'clock a.m. there was no carpopedal spasm. Chvostek, 0. Trousseau, +.

Electrical Reactions:	C. C.	A. C.	A. O.	C. C. T.
	0·8	4·0	2·8	>5

Calcium in the serum, 8·9 mg. per 100 c.c.
July 22. Trousseau, −.

Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	0·9	4·0	3·0	>5

Child seemed entirely normal except for pus in the urine, which had become acid.

July 23. Electrical Reactions:	C. C.	A. C.	A. O.	C. O.
	2·0	>5	>5	>5

It was noticed on this morning that the child was fretful when touched, but was rather drowsy and showed marked hyperpnoea. Blood serum by the dialysis-indicator method: pH, −6·8; RpH, −6·9.

Calcium in the serum, 10·2 mg. per 100 c.c.

Phosphorus, 6·2 mg. per 100 c.c.

At this time there was no acetone to be determined in the breath. Acetone bodies in the blood, 26·8 mg. per 100 c.c. An injection of 175 c.c. of 4 per cent. sodium bicarbonate solution was given intravenously. The calcium was discontinued. At 2 p.m. the hyperpnoea was still very marked. Blood serum: pH, 7·4; RpH, 7·8. Another injection of 175 c.c. 4 per cent. soda solution was given. Shortly after this she began to improve. The hyperpnoea almost entirely disappeared. Sodium bicarbonate was ordered by mouth, grm. 4 q. 4 h. At this time acetone in the breath was present in very large amount (Scott-Wilson reagent) and the acetone bodies in the blood were 111·1 mg. per 100 c.c. *Calcium* 8·7 mg. per 100 c.c. The soda was reduced to grm. 1·0 q. 4 h. after three doses of a larger amount had been given. At 4 p.m. 25 grm. of dextrose and sucrose āā were given in orange juice. Child quiet and comfortable during the night

July 24. In the morning her hands had again assumed a tetany position.

Electrical Reactions:	C. C.	A. C.	A. O.	C. C. T.
	0·3	1·3	0·9	2·0

The soda was reduced to grm. 1·0 t. i. d. While the carpopedal spasm promptly disappeared the Trousseau sign remained present and the C. O. C. remained at a point less than 5 milliampères until August 3, when the Trousseau sign was no longer obtainable. The same day the urine became acid and the electrical reactions were:

C. C.	A. C.	A. O.	C. O.
1·4	3·0	2·5	>5

The onset of symptoms of tetany following the administration of soda and their prompt cessation when the soda was stopped, with the changes in the calcium content of the serum and the electrical reactions, indicate that soda is capable of producing these symptoms.

It is apparent that the symptoms of tetany and the lowering of the calcium content of the serum may be produced in a variety of ways, but we have not been able to show that any of these means is operative in uncomplicated infantile tetany.

Magnesium of the Blood in Tetany.

Calcium and magnesium, both constituents of the serum, are chemically closely related, and from the physiological standpoint it has been shown that their action is frequently similar, though at times it may be distinctly antagonistic. For this reason it appeared advisable to determine also the magnesium in the serum. It was necessary to devise a special method for this, as the amount in the serum is so small that gravimetric determinations are out of the question. This we have done (37). The method is sufficiently accurate to determine the magnesium in 2 c.c. of serum with an error of not more than 5 per cent. The determination may be made with the same sample of serum in which the calcium is determined. It has been found that the amount of magnesium in the serum shows but little variation. Not only is this true during health, but it is also true in disease. We have not found less than 1·75 mg. or more than 4·0 mg. of magnesium per 100 c.c. of serum. The slight variations in the magnesium seem to bear no relationship to the alterations in the calcium, as Table V shows. It is therefore possible to say that magnesium plays no determining rôle in the production of the symptoms of tetany.

TABLE V. *Calcium and Magnesium in Serum expressed as Milligrams per 100 c.c.*

Patient.	Age.	Date.	Condition.	Calcium.	Magnesium.
Placental blood	—	5/28	—	—	2·7
Placental blood	—	5/28	—	—	3·5
R. G.	7 months	5/21	Convulsions, cause unknown	9·6	2·6
H. B.	7 months	4/11	Convulsions, cause unknown	9·2	2·2
C. de F.	1 year	6/4	Petit mal	11·0	2·7
—	Adult	4/19	Normal	9·8	2·8
—	Adult	4/19	Normal	10·5	2·2
R. Q.	1 year	3/17	Mild rickets	9·8	1·75
D. S.	4 months	3/19	Active rickets	9·0	2·6
S. J.	2 years	3/20	Severe rickets	9·3	2·5
G. D.	4 months	3/21	Active rickets	8·0	2·5
C. F.	6 months	4/12	Active rickets	7·9	1·95
H. L.	4 months	4/18	Active rickets	8·2	2·2
S. G.	5 months	5/22	Mild rickets	8·2	3·5
M. S.	6 months	3/17	Active tetany	4·5	1·9
G. S.	5 months	4/3	Active tetany	3·5	2·7
H. H.	6 months	4/10	Active tetany	5·8	3·0
V. F.	6 months	6/11	Active tetany	4·6	2·7
E. S.	22 months	6/11	Relapsing tetany	7·3	2·7
A. B.	9 months	5/24	Tetany after soda	6·0	2·2
N. F.	6 months	3/12	Convalescent tetany	8·5	2·3
M. S.	6 months	3/22	Convalescent tetany	7·0	2·2
M. S.	6 months	3/29	Convalescent tetany	8·5	1·75
H. H.	6 months	4/17	Convalescent tetany	7·5	2·2
G. S.	5 months	—	Convalescent tetany	7·5	2·2
S. J.	9 months	5/22	Convalescent tetany	8·0	2·7
S. J.	9 months	5/28	Convalescent tetany	8·0	3·0
E. S.	21 months	5/28	Convalescent tetany	8·2	2·3
V. F.	6 months	6/18	Convalescent tetany	8·0	2·7

Significance of the Electrical Reactions.

Our results are sufficiently numerous to allow certain conclusions to be drawn regarding the specificity of the electrical reactions of tetany. In Table VI are shown, in parallel columns, the electrical reactions and calcium determinations made at the same time.

TABLE VI. *Active Tetany.*

Calcium expressed as Milligrams per 100 c.c. of Serum.[1]

Age.	Electrical Reactions.				Calcium.
	C.C.	A.C.	A.O.	C.O.	
8 months	0·8	2·0	0·8	4·5	6·0
5 months	0·4	3·0	1·0	4·5	5·7
9 months	0·8	1·8	1·1	2·0	5·5
13 months	0·5	3·2	1·6	3·6	5·0
5 months	0·3	0·4	1·1	1·5	5·0
3 years and 4 months	0·3	2·5	0·7	2·0	5·8
5 months	1·0	3·0	1·0	3·4	3·5
6 months	0·1	0·8	0·5	1·0	5·0
7 months	0·6	4·8	1·1	4·8	6·3
8 months	0·2	1·6	0·5	1·4	4·5
6½ months	0·4	0·5	0·6	0·9	4·7
6 months	0·8	3·4	2·0	4·8	5·8
2½ years	0·1	0·8	0·5	< 4	6·0
21 months	0·2	1·0	1·0	2·4	6·15
22 months	0·8	2·0	1·2	2·5	6·3
7 months	0·4	1·2	0·8	1·8	6·3
7 months	0·4	2·0	1·2	4·0	6·8
				C.C.T.	
8 months	0·5	1·5	1·0	3·0	6·0
17 months	0·8	2·0	1·6	4·0	7·3
				C.C.T.	
6 months	0·6	2·2	0·8	1·3	5·0
5 months	1·4	2·1	1·0	4·5	4·6

It will be seen that in all instances when the C.O.C. or C.C.T. occurred with a current of less than five milliampères, there were unmistakable evidences of tetany and a very distinct reduction in the calcium of the serum. This is another way of demonstrating the specificity of the cathodal hyperexcitability of Thiemich and Mann (11, 12), which, from clinical experience, has been considered satisfactory evidence of the presence of tetany. Regarding the deductions properly to be drawn from the anodal hyperexcitability of von Pirquet (13), there is less unanimity of opinion. It is not such a very uncommon finding with children who are normal, so far as can be made out from the history and from physical examination. We believe, however, that in a considerable pro-

portion of the cases anodal hyperexcitability indicates some disturbance in the calcium metabolism, for although many of the children with anodal hyperexcitability whom we have investigated have never shown any evidences of tetany, they have had, with two exceptions, a calcium content of the serum less than can be regarded as normal. Those children with rickets or other diseases who have had no anodal hyperexcitability have, with two exceptions, had a calcium content of the serum greater than 10·0 mg. Further, children who have had a frank tetany with cathodal hyperexcitability, and who have recovered or improved, have lost their cathodal hyperexcitability but retained an anodal hyperexcitability for a considerable length of time; during this period of anodal hyperexcitability the calcium content of the serum has remained somewhat below normal. These facts are brought out in the following tables:

TABLE VII. *Anodal Hyperexcitability with Calcium below Normal.*

Calcium expressed in Milligrams per 100 c.c. of Serum.

Age.		Electrical Reactions.				Calcium.
		C.C.	A.C.	A.O.	C.O.	
4 months	Active rickets	1·0	4·0	2·5	>5	9·0
1 year	Very mild rickets	1·2	4·2	1·2	>5	9·8
4 months	Active rickets	2·0	>5	3·4	>5	9·0
4 months	Active rickets	1·2	4·2	2·6	>5	9·0
4 months	Active rickets	1·8	>5	2·6	>5	7·9
6½ months	Moderate rickets	2·0	4·6	3·4	>5	8·6
7 months	Moderate rickets	1·0	>5	3·8	>5	9·2
8 months	Moderate rickets	1·4	>5	3·0	>5	9·6
6 months	Convulsions, cause unknown	1·6	4·0	3·5	>5	10·7
5 months	Neuropathic	1·2	4·2	3·2	>5	10·7

TABLE VIII. *Anodal Hyperexcitability in Convalescent Tetany.*

Calcium expressed in Milligrams per 100 c.c. of Serum.

Age.	Electrical Reactions.				Calcium.
	C.C.	A.C.	A.O.	C.O.	
5 months	1·8	>5	4·5	>5	7·5
10 months	2·0	>5	4·0	>5	8·0
13 months	2·0	>5	3·0	>5	7·0
8 months	1·4	>5	2·8	>5	8·5
21 months	1·6	2·6	2·2	>5	8·2
7 months	1·8	>5	3·5	>5	9·0
4 years 9 months	0·8	4·0	2·8	>5	8·9

That anodal hyperexcitability does not necessarily indicate the development of the symptoms of tetany, and that it is found with apparently perfectly normal infants who continue normal, are undoubtedly true, as Holmes (14) pointed out from the clinical study of patients. It is also true, as we have shown, that

anodal hyperexcitability may be found with a quite normal calcium content of the serum. It cannot, therefore, be considered complete evidence of tetany. But as patients probably demonstrate an anodal hyperexcitability before they do a cathodal hyperexcitability, and as during convalescence from tetany they surely lose their cathodal irritability first and continue with an anodal irritability for some time, and as with the majority of infants who have been shown to have an anodal hyperexcitability we have demonstrated a calcium content of the serum less than normal, it is our opinion that anodal hyperexcitability in an infant should awaken the suspicion of a lowered calcium content and therefore a tendency towards tetany.

Calcium Treatment of Tetany.

The influence of calcium upon the symptoms of tetany has been studied in two ways. The first method which has already been mentioned was employed in an endeavour to disprove Stoeltzner's hypothesis. Bogen (25), Risel (26), Rosenstern (27), von Pirquet (13), Zybell (28), and others gave calcium in various forms and in various doses; but they gave usually only one dose and determined the effect of its administration upon the electrical reactions. From the single dose no effect, or only a temporary effect, upon the clinical symptoms was observed. Others, notably Netter (41) and Göppert (42), have consistently used calcium in the treatment of tetany and have reported striking results from its use, when repeated doses have been administered. Its usefulness has not been demonstrated except by the dissipation of clinical symptoms, i.e. its effect upon the electrical reactions or upon the other signs has not been noted. With the proof that in active tetany the calcium in the serum is consistently low, it has been the logical thing to give calcium and to give calcium repeatedly; for if there is a constant calcium loss, as has been shown by Schabad (30) and others, it is only by the continued administration of calcium that a sufficient quantity to prevent symptoms can be kept circulating in the blood. If the administration of calcium is interrupted it soon sinks again to its previous low level. We have, therefore, given calcium by mouth in doses of from 0·5 grm. to 1·0 grm. every four hours. We have also determined the effect of this administration of calcium upon the electrical reactions and upon the calcium content of the serum as well as upon the clinical symptoms. *It may be stated without reservation that calcium has a very prompt effect in preventing all of the symptoms of active tetany.* In the course of a few hours the symptoms diminish in intensity, and almost always in thirty-six or forty-eight hours they have entirely disappeared. The electrical reactions also undergo an alteration so that C. C. T. or a C. O. C. with a current of less than five milliampères is no longer obtained. The calcium content of the serum also rises. In some instances it has reached nearly normal in the course of a few days. In the majority of instances, however, it has not reached normal, but has remained between 7·5 and 9 mg. for

a long time despite the continued administration of calcium. The symptoms, however, have been held entirely in abeyance. We know of hardly another drug which acts in disease with the promptness and with the regularity that calcium does in tetany. The calcium administration must, however, be continued. The cessation of the drug for a few days, perhaps even hours, will allow the return of symptoms, as Case XII (Sykes) demonstrates, and it is altogether probable that in many instances it must be continued until in the ordinary course of events the tendency to tetany disappears. This is added evidence to us that the calcium deficiency in tetany is not a primary condition. It is brought about by some unknown factor which diminishes to a very marked degree the calcium content of the serum, which is operative chiefly during certain months of the year and which gradually loses its effect or disappears. We present in Table IX the effect of calcium administration upon the calcium content of the serum and upon the electrical reactions.

TABLE IX. *Effect of the Administration of Calcium.*

Patient.	Age.	Date.	Electrical Reactions.				Calcium in Serum.	Symptoms and Medication.
			C.C.	A.C.	A.O.	C.O.		
F. A.	7 months	4/21	0·4	2·0	1·2	4·0	6·8	Convulsions. $CaCl_2$, grm. 0·5 q. 4 h.
„	„	4/27	1·8	> 5	3·5	> 5	9·0	No symptoms
						C.C.T.		
A. B.	9 months	5/24	0·2	1·0	0·6	1·4	6·0	Tetany following soda. Soda discontinued. $CaCl_2$, grm. 1·0 q. 4 h.
„	„	5/26	2·5	> 5	> 5	> 5	10·0	No symptoms
N. F.	6 months	3/7	0·2	1·0	0·4	2·5	5·25	Convulsions. Carpopedal and laryngospasm. 3/10 $CaCl_2$, grm. 0·5 q. 4 h.
„	„	3/12	3·6	4·8	> 5	> 5	8·5	No more symptoms
V. F.	6 months	6/11	1·4	2·1	1·0	4·5	4·6	Convulsions. $CaCl_2$, grm. 0·5 q. 4 h.
„	„	6/18	1·8	> 5	> 5	> 5	8·0	No convulsions
H. H.	6 months	3/9	0·8	3·4	2·0	4·8	5·8	Convulsions. 3/10 $CaCl_2$, grm. 0·5 q. 4 h.
„	„	4/17	2·0	> 5	> 5	> 5	7·5	$CaCl_2$ continued but no symptoms
„	„	4/20	2·0	> 5	4·0	> 5	9·0	
S. J.	9 months	4/30	0·8	1·8	1·1	2·0	5·5	Repeated convulsions. $CaCl_2$, grm. 0·5 q. 4 h.
„	„	5/4	1·2	> 5	3·8	> 5	—	No convulsions or other symptoms of tetany
„	„	5/22	2·2	5·0	> 5	> 5	8·5	No convulsions after calcium was given
I. J.	18 months	3/20	0·4	0·5	0·6	0·9	4·6	Convulsions. Carpopedal spasm. Trousseau +. 3/21 $CaCl_2$, grm. 0·5 q. 4 h.
„	„	3/26	2·4	2·8	> 5	> 5	8·45	

TABLE IX (*continued*).

Patient.	Age.	Date.	Electrical Reactions.				Calcium in Serum.	Symptoms and Medication.
			C.C.	A.C.	A.O.	C.O.		
E. N.	13 months	4/23	0·5	3·2	1·6	3·6	5·0	Convulsions. Carpopedal spasm and laryngospasm. Trousseau +. $CaCl_2$, grm. 0·5 q. 4 h.
,,	,,	4/27	2·0	>5	3·0	>5	7·0	No more convulsions after calcium
G. S.	5 months	4/3	1·0	3·2	1·0	3·4	3·5	Convulsions and pneumonia. 4/5 $CaCl_2$, grm. 1·0 q. 4 h.
,,	,,	4/15	2·2	>5	>5	>5	7·5	No further convulsions. Died as result of pneumonia
M. S.	6 months	1/21	0·1	0·8	0·5	1·0	5·0	Carpopedal and laryngospasm
,,	,,	2/13	0·6	4·8	1·1	4·8	6·3	Continued symptoms
,,	7½ months	3/9			—		5·0	Continued symptoms
,,	8 months	3/17	0·2	1·6	0·5	1·4	4·5	Convulsions. Calcium lactate, grm. 1·0 t. i. d.
,,	,,	3/22	0·4	2·8	1·2	2·8	7·0	Calcium lactate discontinued. $CaCl_2$, grm. 0·5 q. 4 h.
,,	,,	3/23	0·8	>5	1·8	>5		
,,	,,	3/29	1·4	>5	2·8	>5	8·5	No symptoms after the administration of calcium
E. S.	21 months	5/8			—		6·5	Carpopedal and laryngospasm
,,	,,	5/18	0·2	1·0	1·0	2·4	6·15	Convulsions. $CaCl_2$, grm. 1·0 q. 4 h.
,,	,,	5/21	0·8	2·8	2·4	>5	—	No more symptoms
,,	,,	5/28	1·6	2·6	2·2	>5	8·2	Calcium discontinued
,,	,,	6/1	0·8	2·0	1·2	2·5	6·3	Pedal and laryngospasm and Trousseau

We employed calcium lactate at first. It did not appear to us that the effects were so prompt as those produced by calcium chloride. For this reason we have given calcium chloride in the great majority of instances. This has been administered in the food. It has not usually been difficult to give it in this way. There has not been marked vomiting with any of the children at any time. We have continued the calcium in most instances for several weeks, and have then gradually diminished the amount and frequency of administration until it was discontinued entirely.

When the calcium has thus been administered we have not seen a return of the symptoms, though it must be admitted that in almost all instances it was continued until the time when one would expect the tetany to disappear in any event, i.e. until the months of May or June.

It is undoubtedly true that in many instances phosphorus and cod-liver oil

have a distinct effect in improving tetany. At times, however, their influence is slight. In any event it is slow, and is often not sufficiently marked or sufficiently prompt to prevent the development of dangerous or perhaps fatal symptoms. Whilst, therefore, these substances are indicated they can by no means take the place of calcium. What their effect is upon the calcium of the serum we propose to investigate at some future time. In the presence of severe or dangerous symptoms, chloral, morphine, and chloroform and magnesium sulphate hypodermically must be used in sufficient amount and frequently enough repeated to hold the symptoms in check until calcium in full doses produces its sedative effect. This is usually within thirty-six or forty-eight hours.[6] Thereafter only the calcium need be given. Further investigations will show whether the influence of phosphorus and cod-liver oil is similar to that of the calcium, and that when its administration is discontinued the calcium in the serum again sinks to a low level, or whether it has a more fundamental effect than the calcium administration and overcomes the factors that are responsible for the deficiency of circulating calcium.

Our conception of tetany is that some factor, at present unknown, causes a reduction of the calcium content of the blood. When this reaches an amount roughly between 6·0 and 7·0 mg. of calcium per 100 c.c. of serum, frank evidences of tetany arise. This amount, however, is not the same with all individuals. With some it may be as low as 5·5 or 6·0; with others, as high as 7·5. These symptoms occur in outbursts so long as the calcium remains low. When the calcium rises the symptoms disappear. The height to which the calcium must rise in order that the symptoms must disappear is also somewhat variable. We believe that many of the symptoms are directly referable to the diminished calcium content of the blood and that they may be prevented or caused to disappear by repeated doses of calcium.

Summary.

The various theories as to the pathogenesis of infantile tetany refer it (*a*) to disease of the parathyroid glands, (*b*) to the character of the food, (*c*) to intoxication by calcium, (*d*) to intoxication by guanidin or methylguanidin, (*e*) to a lack of calcium. The evidence at present available fails to confirm the majority of these theories. We have approached the problem from the standpoint of the calcium content of the blood serum.

By a method which we have devised we have been able to show that the normal calcium content of the serum is from 10 to 11 mg. per 100 c.c.

In rickets there is a moderate reduction of the calcium in some cases (to 8 mg.), but a number of the apparently active cases which we have studied have shown a normal amount of calcium.

[6] We have not used calcium intravenously. There is every reason to believe that its effect would be satisfactory and prompt and, with proper precautions, without danger. We shall make experiments with this method of administration.

In tetany, during the active symptoms, the calcium of the serum invariably is greatly reduced and may fall as low as 3·5 mg. The average calcium content of the serum in eighteen cases was 5·6 mg.

In convulsive disorders other than tetany there is no reduction in the calcium of the serum.

The cause of the calcium reduction in tetany has not been explained. The inorganic phosphates of the serum are not significantly increased.

The magnesium of the serum in active tetany is within normal limits.

Tetany results at times from the administration of large amounts of sodium bicarbonate. We have found no evidence that 'alkalosis' is a factor in the production of infantile tetany.

Cathodal hyperexcitability has invariably been accompanied by a marked reduction of the calcium of the serum.

Anodal hyperexcitability has been accompanied, in the majority of instances, by a slight reduction of the calcium of the serum.

Calcium administration produces a prompt effect upon the course of tetany. In a few hours the spasmodic symptoms disappear. The calcium must be continued, however, for a long time.

Calcium chloride administered by mouth causes an increase in the calcium of the serum coincident with the cessation of symptoms, although, in most instances, the calcium of the serum does not return to quite normal figures.

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ON THE 'DEFICIENCY THEORY' OF THE ORIGIN OF BERI-BERI IN THE LIGHT OF CLINICAL AND EXPERIMENTAL OBSERVATIONS ON THE DISEASE, WITH AN ACCOUNT OF A SERIES OF FORTY CASES

By F. M. R. WALSHE

During 1916 there occurred the opportunity of seeing, in the General Hospitals of Alexandria, a number of cases of multiple neuritis in men invalided from Mesopotamia. Passing over the few of these directly attributable to such causes as diphtheria and arsenic poisoning, and which were readily distinguishable, there remained a large series of cases of obscure aetiology, giving, however, so characteristic a medical history, and presenting so constant a clinical picture, that it was obvious they possessed a common causation.

It is clear that there is a danger in attempting to formulate precise views as to the nature of any disease from the study of a residual paralysis left after its active phase has passed. Still, it is reasonable to say, without being committed to any theory as to the aetiology of these cases, that in their clinical history and physical signs they more closely resembled the residual neuritis of beri-beri than any other clinical type of multiple neuritis.

Owing, therefore, to the very definite views which have gained acceptance as to the cause of beri-beri, the study of these cases assumed a practical importance. Of the 40 cases examined, 15 arose in one unit at the same time and place, and as several of these were accompanied by case records dating from their first admission into hospital, they clearly constituted a valuable series, and helped to confirm the unsupported clinical histories of the rest.

I propose, therefore, after a brief clinical *résumé* of the condition, to give an analysis of this series. The disease occurred in men who had been for three months or over in Mesopotamia. Of the total number, 12 expressed themselves as having had no illness previously during their service in the country. Seven had had 'malaria' either immediately before or during the first week of the illness; while 10 stated that they had had gastro-intestinal disorders, which they spoke of loosely as 'diarrhoea', 'enteritis', or 'dysentery'. Two had had 'heatstroke' during the summer preceding, and two stated they had had 'jaundice'. In many no definite information was obtained. Since, in the majority of instances, no confirmation was available of these statements, no conclusions can be drawn from data so equivocal.

[Q. J. M., July, 1918.]

In every case the onset was subacute, and after an inconstant prodromal period of indefinite unfitness for exertion there appeared, more or less simultaneously, weakness, aching, numbness, and swelling of the legs, with breathlessness and palpitation on exertion. All these symptoms increased rapidly, and in most instances necessitated sending the men to hospital within a week or ten days of their appearance. In one case, that of a man employed as a store clerk, i.e. in a sedentary occupation, the patient was able to carry on for ten weeks until slowly increasing weakness disabled him. Many of the cases complained of a distressing feeling of constriction in the chest on exertion. The oedema in many instances invaded the abdominal wall, but does not appear to have involved the scrotum or penis. Numbness, i.e. loss of sensation, spread equally high, and paraesthesiae, i.e. 'pins and needles', and muscle pains were constant. The loss of power in the legs in some cases was almost complete, in others walking with assistance was possible throughout.

In about a fifth of the cases, the upper limbs were similarly but less severely affected, the chief symptoms noted being difficulty in writing or in doing up buttons and 'pins and needles' in the fingers. In no case was there any cranial nerve involvement and the sphincters were untouched. There appear to have been no mental symptoms, nor any evidence of initial pyrexia or other constitutional disturbance.

On admission to hospital, the cardio-vascular symptoms soon cleared up, leaving the patient with a more or less profound flaccid palsy of the legs, with a corresponding degree of sensory loss, and, in the severer examples, with a progressive wasting of the paralysed muscles, which remained painful.

When, three or four months later, these cases arrived in Egypt there was found, as might be expected from this history, a residual multiple neuritis in which the lower limbs were predominantly affected. The most severe cases showed marked weakness and wasting and tenderness of the muscles. The dorsiflexors were especially picked out in this, as in other forms of polyneuritis, giving rise to footdrop and a tendency to steppage gait. The weakness of the hip-muscles was expressed in the so-called 'squatting test'. The least marked and the most recovered cases showed only weakness of dorsiflexion and some muscle tenderness.

Sensory loss varied in recent cases with the motor loss, and there was impairment of all forms of sensibility, increasing distally and often complete below the knees. In cases in which return of sensation had occurred, only deep sensibility was definitely affected.

The reflexes were, at first sight, less uniformly affected. The severe cases showed almost constantly diminished or absent knee-jerks and absent ankle-jerks; while in many instances in which the knee-jerks remained brisk the ankle-jerks were sluggish or gone—very few indeed show brisk ankle-jerks. Usually the return of the tendon-jerks is the last phenomenon of recovery in polyneuritis, and their presence in some of these cases was astonishing. Slight oedema occurred in some if they were unduly active.

The cranial nerves were always normal, and none of the cases showed any definite cardiac involvement.

An analysis of the series of cases mentioned earlier is of the greatest interest. The unit to which they belonged had been up the line with the Kut relief force in the spring of 1916, but in July were brought to a desert camp twelve miles from Basra and the river. It was still there when the present epidemic occurred. As far as can be ascertained, the health of the unit was good on the whole from July till the cases began to occur in November, and *all the men had been in the camp since July.*

During this period 5 had been free from all illness, 6 had malaria during November or December—in 4 of them the benign tertian parasite is recorded as having been found in the blood.

During the same period the diet of the unit was as follows (all the men gave, independently, consistent evidence on this point, differing in minor details only):

BREAKFAST.—Bacon, porridge, bread and jam; tea and tinned milk.

MIDDAY.—Bread and jam, and a ration of rice several days weekly.

DINNER (7 p.m.).—Beef or mutton, stewed.
Dried potatoes occasionally.
Onions occasionally.

Occasionally, also, melons, cucumbers, haricot beans, and, according to some men, radishes and egg-plant.

During the latter half of November then, in these circumstances, a number of men went sick with the following symptoms of approximately a week's duration: Numbness, tingling, swelling, aching, and weakness of the legs, with palpitation and breathlessness on exertion. An example will serve to show the condition as it occurred in them all.

Pte. L. In Mesopotamia since the previous June, and in good health all the time. On November 14 he noticed a slight aching of the legs after a march, and during the following week there developed the symptoms enumerated above.

On November 24, in hospital in Mesopotamia, these observations were made: Oedema of legs. Pulse-rate 110. First heart-sound weak, with apical systolic bruit. Urine normal. Knee-jerks ? absent.

December 1. Heart as before, oedema less.

Complained of numbness and tingling of legs and abdominal wall.

Knee-jerks absent. Sensory loss and paraesthesiae.

December 22 (Bombay). No oedema. Heart-rate normal, bruit still present. Shuffling gait with weakness of legs, loss of feeling and pain in the calves—stated that he was improving.

On admission to 17 General Hospital, January 18:

Heart-rate normal, occasional dropped beat. No bruit.

Slight oedema round ankles, tenderness of calves and moderate weakness of legs with dropped foot. Sensory loss marked up to thighs. Tendon-jerks in lower limbs absent.

On January 28 the knee-jerks were obtainable with reinforcement.

II. *Beri-beri and Jaundice.*

It is necessary to consider the relationship in which these cases stand to beri-beri of dietary origin. Another possibility must, however, first be considered. Recently, in connexion with cases similar to those described in this paper, Willcox (25) and Hurst (20) have suggested a causal relationship of epidemic jaundice to multiple neuritis. Hurst, recalling the duodenal infection hypothesis of Hamilton Wright (16), says 'it is impossible to explain the outbreak of the disease at Gallipoli solely as the result of a deficiency in the diet'. He compares the supposed relationship between jaundice and neuritis with that between diphtheria and post-diphtheritic neuritis. Cases of neuritis preceded by a vague history of gastro-intestinal symptoms but no jaundice are described as 'neuritis with latent jaundice', while those of jaundice followed by equally equivocal signs, such as tachycardia, tremors, weakness (reflexes not mentioned), are classed as 'jaundice with latent neuritis'.

From these unconvincing speculations it is concluded that 'it seems highly probable that the beri-beri among the troops in Gallipoli was due to a similar duodenal infection to that described by Hamilton Wright, though deficiency in the anti-beri-beri vitamines was probably a contributory factor.'

It is difficult to understand such a position, for if infection be the cause, the 'vitamine' theory can have no place in the pathology of the disease, while if 'vitamine' deficiency is the cause and 'vitamine'-containing foods are adequate protection, it is superfluous to invoke duodenal infection.

Did jaundice and beri-beri stand in any relationship, the latter disease must have been very common in Egypt during the prevalence of epidemic jaundice, yet it is doubtful if a single case originated in the country. In Gallipoli also the disparity between the incidence of the two diseases was extreme and we are scarcely justified in speaking of an 'outbreak' of beri-beri there.

This reversion to the infection theory of the origin of beri-beri need not, therefore, be taken seriously. Of the 40 cases analysed here only two gave a definite history of jaundice, and we must therefore consider them in the light of the 'deficiency' theory of beri-beri.

III. *Beri-beri as a Deficiency Disease: Preliminary Considerations.*

A study of the subject, however, shows that even in the comparatively simple case of the beri-beri associated with a polished rice diet, in which the disease is manifestly dependent on the diet, there are certain difficulties in accepting the view as it is at present formulated that beri-beri is directly due to the *absence* of a certain unknown but essential constituent in the food; that is, to starvation in respect of a specific substance.

It is a well-known physiological observation, that a diet which is adequate in respect of its protein, fat, and carbohydrate content, its salts and its caloric value, may yet be inadequate to permit growth or maintain life.

The well-known experiments of Hopkins (19) are the best examples of this. There exist certain unknown 'accessory factors' in diet which appear to be essential to the organism. In Hopkins's experiments such an 'accessory factor' was obtained from fresh milk, from a protein-free alcoholic extract of milk, or an ether extract of the dried alcoholic extract, or, finally, from a boiled watery infusion of mangolds. These bodies appear active in minute quantities and are of unknown physical and chemical characters.

Their function cannot be to satisfy the energy or nitrogen requirements of the organism, and it seems probable that they have a 'catalytic or stimulating' action (Hopkins) or are 'hormones' (Bayliss).

In his book on Beri-beri, Vedder (23) states: 'An entirely new conception has been given to medicine by the work of Holst, Funk, and the later investigators of beri-beri: the conception of the vitamine. The discovery of these substances is bound to produce a revolution in existing theories of metabolism, for such substances have been undreamed of by physiologists. In the past the value of a food has been estimated by its content in fats, proteids, carbohydrate, and inorganic salts, and by its caloric equivalent'.

This does scant justice to the physiologists, for from a theoretical point of view we know very little more of the 'accessory food factors' than they have taught us. As Bayliss (2) records, as far back as 1880 it was found by Lunin that a synthetic diet, theoretically physiological, might be in fact inadequate to maintain life. Bayliss says, 'As it was pointed out by Starling and myself and by Hopkins independently in 1906, it is not sufficient to estimate the value of a diet, as to whether it is an adequate one or not, merely by its caloric value or its content in fat, carbohydrate, and protein; the presence or absence of the small quantity of the "accessory factors" or "hormones" must also be taken into account'.

Beri-beri and scurvy are therefore regarded as associated with the absence of similar 'accessory factors' in food. Up to this point we may accept the 'deficiency' theory, but we have by no means reached a complete elucidation of the problem, and certain difficulties arise when we attempt to interpret the facts of beri-beri in the light of this theory.

Of the physical and chemical properties of 'vitamines' we know extremely little. Our only certain test of their presence is their physiological effect. Of their mode of action even less is certain, while, as we shall see later, their supposed specificity—that is, the existence of specific 'anti-beri-beri' and 'anti-scorbutic vitamines'—does not entirely accord with certain observations of Holst and Fröhlich.

Further, the relationship of 'deficiency diseases' to pure starvation, also an avitaminic condition, is equally obscure. It is clear, therefore, that the word 'vitamine' rather expresses a conception than represents actual knowledge. It seems necessary to emphasize this when, on an insecure chemical and clinical basis, we find writers postulating a plurality of 'vitamines' in connexion with beri-beri and ascribing to the absence of each a share in the symptomatology of

the disease; to the lack of one, cardiac hypertrophy; to the absence of another, multiple neuritis (Vedder).

IV. *The Properties and Probable Nature of Vitamines.*

The occurrence in poultry, when exclusively fed on polished rice, of polyneuritis, and the undoubted analogy of this disease with beri-beri in every respect, has permitted very precise studies of the aetiology of the disease, and most of the investigations on 'vitamines' have been carried out on experimental birds—fowls and pigeons. In this way the natural distribution of the 'anti-neuritic vitamines' has been ascertained by various workers, notably Holst, Fröhlich, Cooper, Funk, and recently and more completely by Chick and Hume.

The extreme importance of this knowledge is apparent when we come to investigate the beri-beri producing potentialities of any diet, such for example as that associated with the cases described here. Chick and Hume (8) have shown that 'the anti-beri-beri vitamine' is extremely widespread, and is found present in a greater or less degree in almost every natural food-stuff investigated. It is most abundant, however, in the seeds of plants and the eggs of animals.

Practically the important point is that the chief source is in cereal grain and edible pulses. The importance of the embryo, or germ, of the seed as the seat of these bodies has been realized by Chick and Hume and appears to have escaped earlier observers. In the rice grain, the embryo contains the largest deposit of 'vitamine', the rest being contained in the aleurone layer and pericarp. The paper of these authors contains a comprehensive list both in respect of 'anti-neuritic' and of 'anti-scorbutic vitamines'.

Since it has also been found that the 'vitamine' is relatively thermolabile it will be seen that a wide range of dietaries may give rise to beri-beri, and considerable care must be taken before we can exclude the dietary origin of an outbreak of a disease resembling beri-beri clinically, and it is clear, in view of these investigations, that the series of cases described here were associated with a diet showing a pronounced lack of 'vitamine'-containing foods, and as such may reasonably be regarded as true beri-beri.

The physical and chemical characters of 'vitamines'. Before we can expect to form any conception of the nature and mode of action of the 'anti-neuritic vitamine' we must have some knowledge of its physical and chemical properties. It is remarkable that when physical chemistry is playing so extensive a part in the solution of physiological and biochemical problems, the study of the 'vitamines' should have been approached solely from the point of view of structural chemistry.

Such facts as we possess concerning the physical characters of the 'anti-beri-beri vitamine' have been acquired incidentally in the course of attempts to isolate a pure organic base, for such it seems to be widely assumed is the substance in question. We know, however, how large and important a rôle is played

in all processes occurring in living tissues by various physical and physico-chemical reactions such as catalytic and adsorption phenomena and reactions peculiar to the colloidal state.

The investigation of the 'vitamines' must, therefore, be approached on somewhat broader lines if we are to determine their nature and mode of action.

Among the points which at once suggest themselves as of significance in this connexion are the thermolability of this 'vitamine', its formation of adsorption compounds, its inactivation in alkaline medium, its lack of any constant chemical structure or reaction, and its efficiency in small quantities.

Whether any, or all, of these characteristics are possessed by the so-called 'anti-scorbutic vitamine' it is impossible to say, no investigations on it, excepting as to its distribution and its thermolability, having been carried out. It may even be questioned whether its distinctness from the 'anti-neuritic vitamine' is as yet finally decided, and this matter will be subsequently discussed. A brief consideration of these characteristics may throw some light on the nature of 'vitamines'. It was first pointed out by Eijkman that boiling at 120° C. for two hours destroyed the active principle in whole rice, and all subsequent work has confirmed this observation. Boiling at 100° C. does not cause destruction of the 'anti-beri-beri vitamine'. Fraser and Stanton found that within narrow limits accompanying physical conditions such as moisture and pressure modified the effect of heat. As regards the so-called 'anti-scorbutic vitamine' Holst and Fröhlich and Chick and Hume find it more thermolabile—being affected appreciably by boiling at 100° C.

An interesting fact recorded by the latter observers is that while the 'anti-beri-beri vitamine' is present in an active form in resting seeds, the 'anti-scorbutic vitamine' is 'deficient in all dry food-stuffs', or it might be more accurate to say it is inactive in these, and is only found in living and active vegetable tissues. It appears in certain germinating seeds from which it was absent or inactive in the resting stage.

As to the solubility of the active 'anti-beri-beri' principle no complete statement can be made. It appears soluble in water and alcohol up to 91 per cent. in strength in acid medium. It is insoluble in ether and is carried down from solution on the addition of phosphotungstic and tannic acids, but whether it is actually precipitated or carried down in an adsorbed state by the other substances actually precipitated cannot be determined. The latter suggestion is the more probable.

All investigators have found it 'destroyed' by alkalis. It may be more correct to state that it is inactivated by these. According to Chamberlain and Vedder (6) it is dialysable through parchment paper, and these observers conclude therefrom that it cannot be colloidal. They also find it readily adsorbed by animal charcoal, or, as they express it, 'possesses a strong affinity for bone black', while Seidell (22) finds that the 'anti-neuritic' principle obtained from yeast forms an adsorption compound with hydrous aluminium silicate. That it is active in small amounts is evident from the work of all the investigators.

Attempts to isolate 'vitamine' from rice polishings and from yeast in a pure state have been uniformly unsuccessful. To a number of organic bases, having little in common chemically, protective properties have been assigned by Funk (vitamine), Edie, Evans, Moore, Simpson and Webster (torulin), Tsuzuki (anti-beri-berin), and Suzuki, Shimamura, and Odake (oryzanin), but the truth is that the more the active principle is purified, the fewer characteristic reactions of any kind does it show, and at the same time the more unstable it becomes. Usually it is found to disappear during the course of the reactions intended to isolate it. Funk himself has finally concluded that it has never been isolated. As Bayliss (2) suggests, Funk's base is not really the active substance, but probably an adsorption compound with the phosphotungstic acid precipitate. This may be considered equally true of the fantastically named substances mentioned above.

No known element can with any certainty be said to form an essential part of its molecule, and, as Fraser and Stanton conclude, the biological test remains the only criterion of its presence.

These facts, fragmentary as they are, suggest a possible nature of the 'anti-beri-beri vitamine'. One cannot help being struck by the fact that these physical and chemical characteristics are pre-eminently those of a well-known group of colloidal substances with a wide distribution in nature; namely, enzymes. It is known that certain enzymes will resist the temperature of boiling water (Bayliss (1)); that Funk's 'vitamine' does so, therefore, does not exclude its belonging to this class of bodies.

That the 'anti-beri-beri vitamine' dialyses through parchment paper does not, as Chamberlain and Vedder state, exclude its being colloidal—a necessary presumption if we are to regard it as being an enzyme. Colloids are not absolutely indiffusible. Congo red, which shows all the usual characters of colloids, will pass slowly through parchment paper. The colloidal aniline dyes exhibit all degrees of diffusibility. While in invertase and diastase we have examples of diffusible enzymes.

The source of 'vitamines' is also of significance in this connexion. Yeast is a well-known source of enzymes, of which glyoxalase, which plays an important part in carbohydrate metabolism, may be specially mentioned here. The castor-oil bean yields a lipase, while certain fruit juices contain proteoclastic enzymes.

Hopkins (19), as mentioned earlier, is of opinion that the 'growth hormones' or 'vitamines' in his experiments were 'of the nature of an organic complex, or complexes, which the animal body cannot synthesize. But the amount which seems sufficient to secure growth is so small that *a catalytic or stimulative function* seems more likely.'

More recently Cole and Jordan Lloyd (9), investigating growth conditions of the gonococcus in artificial media, have found that 'special growth hormones' or 'vitamines' play an important part. Their observations are most suggestive from the point of view of the physical chemistry of these bodies, and show

that this aspect of the question is, as has been emphasized here, of the greatest importance.

It is probable that the 'vitamines' associated with beri-beri and scurvy possess the same characters and catalytic functions as the 'accessory factors' of Hopkins and these authors. Therefore, although further and more broadly conceived researches are necessary before we can hope to solve the problem of the nature of 'vitamines', this conception of them as enzymes may well be considered. It accords far better with the physiological view of the nature of accessory food factors in general than the narrow structural chemical hypothesis at present favoured by workers in this field.

V. *The Relationship of the Deficiency Diseases to Starvation.*

The relationship between starvation and the deficiency diseases has been the subject of numerous investigations, the results of which are held to accord with the 'vitamine' theory of the origin of these diseases. It is stated that general starvation is not productive of beri-beri or scurvy. Thus, Fraser and Stanton (12) say that 'polyneuritis in fowls is not due to general deprivation of food, but to deprivation of some particular element in polished rice', while Holst and Fröhlich (18) state that 'it is thus evident that scurvy *cannot* be caused in guinea-pigs by simple starvation or diets of *any* kind; on the contrary, the disease originates in these animals as well as in man as a result only of certain special diet'.

Now, the 'deficiency' theory of the origin of beri-beri and scurvy involves but a single negative factor in the production of these diseases; namely, the absence of a specific 'vitamine' in each case. Since, then, in this essential respect starvation is the equivalent of an avitaminic diet, it would be expected that birds starved completely, provided that they survived sufficiently long under such conditions, should show signs of polyneuritis. Actually, this does not occur, and it is difficult, therefore, to see how the 'deficiency' theory in its present form can be maintained.

The experiments undertaken to elucidate this point by various workers fall into three classes and will be considered accordingly.

(i) *Feeding experiments on fowls with starvation rations of whole rice.* The rice used in these, being of the undermilled variety, does not produce neuritis, and Eijkman found that fowls fed on various starvation allowances of this constantly died without the development of polyneuritis. Holst (17) has confirmed these results. Considered in the light of certain observations of Fraser and Stanton (12) these experiments are highly significant. These authors find that an adult fowl of from 1,200–1,400 grm. requires 60 grm. of undermilled rice daily or the same amount of the polished variety with the addition of 5 grm. of polishings. They estimate that 25 grm. of polished rice correspond to

5 grm. of polishings.[1] And since this latter is the physiological minimum of this 'vitamine'-containing substance, fowls fed on less than 30 grm. of undermilled rice are ingesting less than the amount of vitamine necessary to protect them from polyneuritis, and should, therefore, according to the current deficiency hypothesis, develop this condition. That they do not, suggests that the amount of 'vitamine' required varies directly with the amount of rice eaten, and not with the body-weight of the fowl. Braddon and Cooper (3) have recently established this point.

(ii) *Feeding experiments on fowls with starvation rations of polished rice.* Numerous important series of experiments have been made under these conditions. Maurer found that, on polished rice, those fowls on the largest rations first developed polyneuritis; by the use of very small amounts its onset could be delayed. Cooper obtained identical results. Funk (14) also made very significant observations. Feeding fowls on the following rations of polished rice, 20, 10, 5, and $\frac{1}{2}$ grm., he found that those on the largest ration developed polyneuritis and died first. Those on 0·5 grm. died later without polyneuritis, and he concluded that diets rich in carbohydrates hasten the onset of the disease. What these observations actually prove is that the absence of both 'vitamines' and polished rice does not cause polyneuritis, but that, in the absence of the former, polished rice directly causes polyneuritis.

(iii) *Complete starvation experiments.* Fraser and Stanton (12) fed 22 fowls on water alone. These birds lived into the fourth and fifth weeks, dying without clinical or post-mortem microscopical evidence of neuritis. A group of fowls concurrently fed on polished rice showed signs of polyneuritis within a similar period. They state that 'fowls receiving nothing but water do not develop polyneuritis, while fowls receiving only polished rice and water do'.

From these sets of observations the following conclusions are inevitable: (1) Complete deprivation of food, and therefore of 'vitamines', does not suffice to cause polyneuritis, although the survival period of starved fowls exceeds the latent period necessary for its development in appropriately fed birds. (2) Polished rice, in the absence of 'vitamines', does directly produce polyneuritis gallinarum and appears an essential condition of its appearance. (3) The amount of 'vitamine' required to prevent the development of polyneuritis appears to vary directly with the amount of rice ingested. (4) There are two factors, which may be called the negative and the positive factors; namely, the absence of 'vitamines' and the presence of something else, essential to the production of polyneuritis. (5) From this it follows that the present 'deficiency' theory, which recognizes a single negative factor as the cause of beri-beri, is not compatible with these experimental observations and cannot be maintained in its present form.

It will be noted that while most authors hold that starvation does not cause the deficiency diseases, they yet maintain the single factor hypothesis,

[1] They say 'from 40 parts of *padi* there are produced 25 parts of rice and 5 parts of polishings; 16 per cent. of the husked grain is thus lost in polishing'.

which regards absence of a specific 'vitamine' as the direct and sole cause of these diseases.

It is not clear how such a position can be logically upheld.

Chamberlain, Bloombergh, and Kilbourne (5), possibly appreciating the contradiction involved in an acceptance of both theory and facts, attempt to explain the discrepancy by supposing that starved fowls must anticipate the development of polyneuritis by death. Fraser and Stanton's observations negative such an idea. Further, it is noteworthy that whereas fowls on polished rice show, according to Vedder and Clark (24), microscopical evidence of nerve degeneration as early as the seventh day on such a diet, Fraser and Stanton's starved fowls showed no such abnormality after four weeks.

While beri-beri and scurvy are definitely dietary in origin in that they are associated with physiologically inadequate diets, the purely negative 'one-sided' starvation explanation of their origin is inaccurate in that it does not recognize the existence of two essential factors in the production of a deficiency disease. These two factors may be stated as follows: (1) the absence of an unknown 'accessory factor' or 'vitamine'; (2) the use of 'certain special diet'. To these we may add, as a corollary, that the absence of both factors—that is, complete starvation—does not produce these diseases. Their aetiology may therefore be more accurately defined thus: '*The use of certain food substances, in the absence of their specific "accessory factors" or "vitamines", directly causes certain diseases of which beri-beri and scurvy may be considered examples.*'

Such a statement recognizes the two factors involved and ascribes to each its proper place in the aetiology. We shall see that this second factor is in all probability constituted by carbohydrates.

Arising out of the rôle of the 'vitamines' in the deficiency diseases is the question of their specific character. The 'vitamines' associated with beri-beri and scurvy are regarded as being separate and distinct bodies. Thus we speak of 'anti-neuritic' and 'anti-scorbutic vitamines'.

The researches of Holst and Fröhlich and of Chick and Hume afford a considerable amount of evidence in favour of such a view. However, certain observations of Holst and Fröhlich conflict with this. For these observers found that certain diets, namely, decorticated rice and barley, which produced polyneuritis in fowls produced, not polyneuritis, but scurvy in guinea-pigs. Thus we find one diet associated in two series of experiments with two distinct diseases. Chick and Hume state of these observations that the diets in question 'contained abundant anti-neuritic vitamine'. That this is not the case is clear from the nature of the diets in question and from the fact that these did actually produce polyneuritis in birds. A large number of guinea-pigs fed on such a dietary all developed scurvy, but not polyneuritis. The details are as follows: 13 fed on barley groats, 6 on polished rice, 8 on wheat-flour bread, and 10 on boiled dried potatoes. In addition 15 were fed on similar diets with fruit juice or cabbage to avert scurvy. All these diets were actually productive of polyneuritis in Holst's series of observations on pigeons and chickens, except

those last mentioned as being modified by the addition of anti-scorbutic elements, and these contain, according to current theories, no anti-neuritic principle. Yet in all these cases only two animals developed polyneuritis. The authors say, 'In contrast to the experiments on pigeons which one of us has described in the foregoing article, we have, however, been able to detect a pronounced polyneuritis in two animals only', and this out of a series of 65 animals.

The occurrence of both polyneuritis and scurvy in fowls and guinea-pigs would be comprehensible, since according to the work of all four observers the diets in question lack both 'vitamines'. If we assume that fowls do not develop scurvy, we still do not escape the difficulty unless we assume that, unlike man at one end of the scale and birds at the other, guinea-pigs are not susceptible to avitaminic polyneuritis. We cannot make assumptions of this kind and can only conclude that the hypothesis of the specificity of 'vitamines', like other aspects of the 'deficiency' theory, is more simple and uncomplicated than the phenomena it purports to interpret.

In two important respects, therefore, the 'deficiency' theory as it is at present formulated is inadequate to account for the facts actually observed, and we must consider to what conclusions these lead us, if indeed there are as yet sufficient data for any final conclusion.

VI. *The Rôle of Carbohydrates in the Production of Beri-beri and the Polyneuritis of Fowls.*

We have now to consider the part played in the production of a deficiency disease by the avitaminic diet, since it is evident that this is an essential factor and plays a positive and direct part in the causation of the condition. Indeed, on general principles it may be questioned whether so negative a cause as the mere absence of any specific food constituent can produce so striking and positive a set of morbid phenomena as a disease like beri-beri presents to us. It is readily comprehensible that there should be essential food constituents without which life cannot be maintained. These are for the most part known to chemists and physiologists and their nature and functions more or less completely understood. To the unknown substances, however, postulated as entirely and directly concerned in the causation of beri-beri and scurvy is assigned a different function by the 'deficiency' theory. This theory involves the existence widely distributed throughout nature of a class of bodies the specific function of which is to prevent the organism from spontaneously, and for no *positive* cause, developing such well-defined and acute morbid conditions as beri-beri and scurvy may be.

Such a conception seems altogether alien to physiological processes as we know them. More consonant with the facts and more reasonable on *a priori* grounds is the hypothesis that certain food-stuffs, in the absence of their specific associated 'accessory factors', become directly harmful to the organism, possibly by an aberrant metabolism, and so cause these diseases.

In considering this direct part played by the avitaminic diet, the feeding experiments of Maurer, Cooper, Funk, and Braddon and Cooper already quoted assume primary importance. They show a direct relationship between the amount of carbohydrate ingested and the development of polyneuritis. In their observations Caspari and Moszkowski (4) and Funk (14) found that a synthetic diet caused polyneuritis more rapidly the greater its carbohydrate content, and Funk concludes, firstly, that increasing amounts of food-stuffs rich in carbohydrates hasten the onset of polyneuritis, and secondly, that the vitamines play a more important part in carbohydrate than in other metabolism and that carbohydrates make a great demand on the vitamine content of the organism. Obsessed by the exclusive importance of 'vitamines' he did not conclude, as he might justifiably have done, that carbohydrates appear to bear a direct causal relationship to beri-beri, apart from 'vitamines'.

In another investigation Funk found that on a polished rice, i.e. an avitaminic diet, pigeons develop a tendency to hyperglycaemia and diminution of liver glycogen. It does not seem yet possible to appreciate the significance of these modest metabolic studies; they have a unique interest in that they constitute the sole study in the chemistry of the metabolism of a disease that is widely spoken of as 'a disorder of metabolism'.

The fact that the physiological minimum of 'vitamine' varies not with the body-weight of the fowls but with the amount of carbohydrate ingested, as suggested by Eijkman's early experiments and now established by Braddon and Cooper (3), demonstrates the direct part played by this food-stuff in the production of polyneuritis.

Further experimental evidence of the significance of carbohydrates is afforded by certain feeding experiments with superheated meat. Grijns fed 8 chickens on beef boiled in an autoclave for two hours at 120° C. Five of these lived for periods up to eleven months, dying without any neuritis. Three lived for 14 days, 15 days, and 5 months respectively, and showed post mortem some nerve degeneration. Eijkman fed three chickens on meat identically treated. One remained healthy at the end of four months. The other two died without neuritis in one and four months respectively.

Holst's feeding experiments also tend to show that on superheated meat polyneuritis gallinarum is not so constant as on polished rice—that is, on a carbohydrate diet.

In the cases of human beri-beri, as in the experimental disease, the facts all tend to show the significance of a carbohydrate diet. Speaking of the relationship of tinned foods to 'ship beri-beri', Holst says that this 'may be of importance in other respects. Such food in the long run is not palatable. The sailors, therefore, as a rule eat little of it. The result is that their diet becomes comparatively *one-sided, consisting chiefly of farinaceous constituents.*' These are a poor white-flour bread, baked without yeast, and dried potatoes, both of which are productive of polyneuritis gallinarum. The association of carbohydrates with the outbreaks of the disease in Newfoundland and Labrador is equally certain.

This factor is very apparent in the classic feeding experiment of Fraser and Stanton on Javanese coolies (11). Of 220 men on white rice staple diet, 20, or roughly 9 per cent., developed beri-beri after an approximate period of 90 days. This diet was as follows:

Polished rice	603 grm.
Potatoes	50 „
Onions	50 „
Dry salt fish	120 „

and various small items such as coco-nut and coco-nut oil, salt, and tea, 72 grm. They estimate the average body-weight of their subjects at 100 lb. and their physiological requirements in food at

Protein 90 grm. Fat 68 grm. Carbohydrate 272 grm.

The diet supplied was found to contain

Protein 91·45 grm. Fat 43·7 grm. Carbohydrate 499·16 grm.

The deficiency in fats increases the relative preponderance of carbohydrate, which is already almost double the physiological standard.

Whether the 'vitamine'-content of the 50 grm. each of onions and potatoes was enough to have any significance is perhaps open to question. The relatively small proportion of men affected suggests that it had. In any case the preponderatingly carbohydrate nature of the diet cannot be questioned. The dietaries on which various outbreaks of the disease have occurred among troops recently may be regarded as showing the same characteristics—a low 'vitamine'-content and a high carbohydrate value. Thus, there is at least considerable evidence that a causal relationship between beri-beri and carbohydrates exists.

It may be objected that we know nothing of any processes by which these may influence the disease. But it is no less true that we know nothing of the action of 'vitamines'. Until the metabolism of the avitaminic disease has been more completely elucidated it must remain impossible accurately to define the relative value of the two factors mentioned in the production of beri-beri.

It is interesting, however, to consider that the probable significance of the second factor now proposed, if we admit its existence, is that beri-beri, while primarily a deficiency disease in that it is associated with inadequate diets, is in its actual nature an intoxication, dependent on an aberrant carbohydrate metabolism.

Such a conception does not constitute a reversion to the old intoxication theories of beri-beri, which involved the ingestion with the rice or other food of some toxin or chemical poison. Further, the evidence regarded as definitely excluding a toxaemic origin of beri-beri by no means excludes an intoxication in the sense now indicated. That the polished rice diet of the Asiatic contains no noxious bodies as eaten does not exclude the subsequent development of toxic characters during hydrolysis and assimilation.

While such a theory may be regarded as speculative, at least it has never

been excluded, and does not appear incompatible with such facts as we do possess. It may, therefore, be suggested that such a diet as that productive of beri-beri in man and polyneuritis in fowls, consisting as it does predominantly of carbohydrates, may, when taken without its corresponding 'accessory food factor', undergo an aberrant metabolism during the course of which certain toxic by- or end-products are formed which are the direct and immediate cause of beri-beri.

VII. *Beri-beri considered as an Intoxication.*

So far evidence has been put forward to show that the present 'one-sided starvation' theory of 'deficiency diseases' is inadequate, and that another factor must be assumed, both from facts and on theoretical grounds, to explain such a disease as beri-beri. Reasons have also been adduced for regarding carbohydrates as the direct and positive cause, the absence of 'vitamines' being the primary and negative cause. It has been suggested, though the fragmentary state of our knowledge of the metabolism of the disease does not allow more than a suggestion, that carbohydrates, in the absence of their specific 'accessory food factor', undergo an aberrant metabolism producing a toxaemia, which is beri-beri.

An examination of the clinical and pathological features of beri-beri should help us to decide whether such an intoxication theory as is now put forward offers a more complete and satisfactory explanation of the disease than the present negative 'deficiency' theory. It is surely justifiable to draw some conclusion as to the possible origin of a disease from its form and its morbid anatomy. In doing so with beri-beri we are on somewhat safer ground than the theories we have been discussing afford us. Clinically, after the subsidence of the initial oedema, the polyneuritis of beri-beri is indistinguishable from the toxic neuritides of alcohol and diphtheria. Pathologically, this is equally true.

From a study of the nervous system in polyneuritis gallinarum (polynévrite avitaminique), Lhermitte (21) concludes that it is clearly a toxic polyneuritis, while the cerebral cortex shows the morbid changes found in the classic psycho-polyneuritis of Korsakow of alcoholic origin. Lhermitte says: 'La constatation de lésions corticales est un trait de plus qui permet de rapprocher la polynévrite alimentaire avitaminique, le béri-béri expérimental, des polynévrites toxiques.' These conclusions of an observer who is unique among writers on the subject, in that he has a wide clinical and pathological experience of other affections of the nervous system than beri-beri, cannot but be regarded as very significant in their bearing on the nature of this disease.

Vedder's (23) conception of beri-beri, which may be taken fairly as representing the modern view, is that 'Funk's vitamine, which prevents the development of the disease . . . is a building stone which is essential for the normal metabolism of nervous tissue. A certain amount of this vitamine is constantly necessary in order to maintain the nervous system in a healthy condition. If

the supply of vitamine is cut down . . . the normal metabolism of the nervous system at once suffers . . . the degeneration of the nervous system progresses steadily until a point is reached at which the symptoms of beri-beri appear.'

With this conception of beri-beri as a diffuse degeneration of the nervous system, let us consider the clinical picture presented by 'acute pernicious beri-beri' or that of the severe polyneuritis which follows the acute non-fatal form, and the total inadequacy of such an hypothesis to account for either clinical phenomena or pathological findings must be at once apparent to every one whose experience of nervous diseases does not begin and end with beri-beri. That the author himself is aware of this is apparent, for, to account for the oedema, the cardiac symptoms, and subsequent cardiac hypertrophy, he is led on unconvincing clinical and chemical grounds to predicate a second 'anti-beri-beri vitamine', the absence of which is responsible for these.

Since in this country the opportunity does not often arise of seeing the disease, an extract from Hamilton Wright's[1] admirable clinical and pathological analysis of beri-beri (16) may be quoted with advantage to emphasize the disparity between the disease and its suggested cause. He says of the acute pernicious form: 'A man who yesterday would have attracted attention because of his fine physical condition will to-day complain of loss of appetite. . . . I have seen cases beginning with the above premonitory syndrome of gastro-duodenal irritation develop within twenty-four hours almost complete flaccid paralysis of nearly all voluntary movements. . . . Even within twelve hours the heart proclaims its release from nervous control. The vessels in the neck, the larger arteries in the limbs, and the epigastrium throb violently and perhaps irregularly. An irregular, massive wave sweeps over the praecardiac area or even over the whole chest with every beat of the heart. . . . The heart, especially on the right side, becomes greatly dilated, the lungs give signs of engorgement, shortness of breath follows, and the patient passes to death through an agony distressful to behold'.

It is difficult to regard such a condition as the result of a slowly progressive nervous system degeneration, and the disease bears a far greater resemblance to a severe toxaemia, varying in intensity in different cases, with a special but by no means exclusive incidence on the nervous system.

There is a tendency among the pathologists of this disease to ascribe all the cardiac phenomena—clinical and post-mortem—to vagus degeneration. This is possibly in part born of the unconscious tendency to adapt the facts of the disease to the procrustean bed of the 'deficiency' theory. In this respect an interesting parallel is afforded by diphtheria, in which it was considered that the acute cardiac failure of the disease was due to degenerative changes, or at least toxic disorders of the vagus. Dudgeon (10), however, has pointed out that primary myocardial change is the cause. It seems extremely probable that this

[1] While Hamilton Wright's views on the aetiology of beri-beri cannot now be accepted, there is no doubt that no other writer has surpassed the admirable precision and comprehensiveness of his clinical and pathological description of the disease (16).

is equally true of beri-beri, which in its neuropathology presents many striking similarities to diphtheritic paralysis.

In the light of the views expressed, a review of the clinical and experimental data suggests the possibility that in beri-beri we are dealing with a toxaemia due to an aberrant carbohydrate metabolism dependent on the absence of an 'accessory factor' which may be in nature an enzyme.

Since, from both Funk's (13) and Braddon and Cooper's (3) observations, a monosaccharide (glucose) as well as the polysaccharides (starch) may be equally productive of polyneuritis gallinarum, such an enzyme must become active during the further hydrolysis of the sugars.

In this connexion it is interesting to recall that an enzyme—glyoxalase—is thought to play an important part in carbohydrate metabolism. This enzyme is found abundantly in yeast—also a potent source of 'anti-neuritic vitamine'.

We may readily conceive the possibility, in the absence from the diet of such an enzyme, which the organism cannot synthesize itself, of an aberrant metabolism resulting in the formation of some toxic by- or end-product productive of such a disease as beri-beri. In this light also we may conceive of the development of active anti-scorbutic powers in seeds during germination as being the formation of an active enzyme from a zymogen, rather than as the formation of an entirely new substance. In fact a wide range of possibilities is opened up by the conception of 'vitamines' as enzymes. This, however, must remain speculation until the physical chemistry of these bodies and the metabolism in beri-beri come to be the subjects of scientific research. We cannot otherwise hope to solve the problem of the deficiency diseases, and the definition given in sect. V of this paper is as much as can be regarded as established at present. There seems a tendency on the part of certain recent writers to adopt a similar view.

Braddon and Cooper (3), in recognizing the significance of carbohydrate in the production of the disease in birds, and Funk's recognition of the same fact, mark a distinct advance in this direction. It is, however, most clearly defined by Williams and Johnson (26), who express the belief that deficiency of 'vitamine', *per se*, is not the cause of beri-beri, the symptoms of which are produced by some unknown toxic substance, possibly by a product of disturbed metabolism for which the 'vitamines' act rather as antidotes than as foods.

VIII. *Summary.*

The series of cases described here, from their clinical aspect and on the grounds of their aetiology, may be regarded as true beri-beri. There is no evidence in support of a recently expressed view that this, or similar outbreaks of the disease described as occurring among troops, bears any relation to epidemic jaundice and is of the nature of an infection.

A consideration of the deficiency theory of the origin of beri-beri in the light of recent clinical and experimental work makes it clear that the present hypo-

thesis, which postulates a single negative factor, namely, the absence of a specific 'accessory food factor' or 'vitamine', is inadequate. It conflicts with the results obtained in starvation experiments on fowls. Starved fowls live sufficiently long to develop the disease (polyneuritis gallinarum) under such conditions, yet they die without developing it, although in this essential respect, namely, the deprivation of 'vitamines', starvation is the equivalent of an avitaminic diet.

The use of 'certain special diet' (Holst) is found to be an essential condition of the production of the disease both in man and poultry.

It is apparent from all recent experimental work, both in man and poultry, that there are two factors in the production of beri-beri: (1) the absence of an 'accessory food factor' or 'vitamine'; (2) the use of certain foods which are the direct and immediate cause of the disease.

There is a considerable weight of evidence to prove that carbohydrates constitute this second direct and immediate factor. It seems probable that in the absence of their specific 'vitamine' they undergo an aberrant hydrolysis with the production of toxic by- or end-products, thus producing beri-beri. Viewed in this light the disease is an intoxication. The facts regarded as excluding a toxic origin of beri-beri do not exclude an intoxication in this sense.

From another point of view, it may be questioned whether the clinical and pathological characters of the disease are compatible with the theory that it is a slowly progressive diffuse degeneration of the nervous system. The striking symptoms of beri-beri and the widespread visceral and nervous changes seen post mortem cannot be adequately accounted for by such an hypothesis.

A consideration of the physical and chemical properties of 'vitamines'—as far as they are known—suggests the probability of their belonging to the class of bodies known as enzymes, and thus are concerned, we may suppose, in the hydrolysis of carbohydrates.

Certain observations of Holst and Fröhlich, showing that a diet of decorticated rice or barley may produce either polyneuritis or scurvy according to whether fowls or guinea-pigs are employed, throw some doubt on the separate identity and specificity of 'anti-neuritic' and 'anti-scorbutic vitamines'.

Finally it seems certain that until the physical chemistry of the 'vitamines' and the metabolism in beri-beri—both totally unexplored fields—have been more fully investigated, the pathogenesis of beri-beri will remain in part obscure. Al we can say is that the theory which regards the absence of 'vitamines', acting by producing a slowly progressive diffuse nervous system degeneration, as the sole and direct cause of beri-beri is both inadequate to explain all the facts and is incompatible with certain of them.

The genesis of the disease may be best expressed by saying that the use of certain food-stuffs, probably carbohydrates, in the absence of their 'accessory food factors' or 'vitamines', directly causes beri-beri.

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THE ARTERIAL AND VENOUS BLOOD PRESSURES IN THE ENTERIC GROUP OF FEVERS

By H. FAIRLEY MARRIS

With Plate 19

'When the human body is invaded by any member of the typhoid group of bacilli so as to give rise to typhoid, paratyphoid A, or paratyphoid B, a toxin is formed which affects the arterioles in a peculiar manner; the presence of this toxin can be detected by the abnormal yet characteristic reaction of adrenalin.'

During the last few years the study of the blood pressure in man has engaged the attention of many observers, but so far the work has been mainly confined to the arterial side of the circulation: observations upon the pressure in the human venous system are comparatively few. It is known that the venous, like the arterial, blood pressure varies with the part of the venous system in which it is taken. Clinically speaking, however, by the term 'arterial blood pressure' is usually understood that in either the brachial or radial arteries, and for the purpose of this paper the term 'venous blood pressure' is used as signifying that in the basilic vein.

It is generally known that changes in the venous blood pressure do occur, and such changes have been produced experimentally upon animals. The paucity of similar studies in man may be accounted for by the lack of any method of making reliable observations. Crude as our knowledge of the arterial pressure within the human body really is, owing to the imperfections of our instruments which only give indirect records, yet it must be admitted that striking advances have been made in this field. A similar advance is lacking in the case of the venous pressure.

In the course of my studies during the course of the last two years, which have been principally devoted to the Enteric Group of Fevers, I have systematically recorded the arterial pressure of my cases. A large number of observations have also been made on the venous pressure throughout the disease. A similar series of records has been obtained from healthy controls.

My desire to investigate the venous blood pressure was brought about by an observation made during the last half-hour of life in a case of typhoid fever. The heart was failing rapidly, and while the case was actually under examination

the superficial veins all over the body were observed to swell up and stand out like whipcords. On performing venesection with a view to relieving the right side of the heart, the blood gushed out, showing a pressure obviously excessive. I there and then decided to devise some simple means by which the venous pressure could be recorded.

Methods adopted for recording the arterial blood pressure. The Leonard Hill modification of the Riva-Rocci apparatus was used, the readings being made by the auscultatory method; this, as is well known, gives figures higher by 3 to 4 mm. than the finger method. With a view to controlling these observations the sympathy of some of my colleagues was enlisted. It was soon apparent that although we agreed upon the point of total disappearance of the sound, we differed somewhat upon that at which it returned, and still more so upon the point at which the sound became muffled prior to its final disappearance, which is stated to be determined by the diastolic pressure. Hence, as yet I hesitate to give diastolic readings, such as are shown were all made by myself alone.

As I concluded that the total disappearance of the sound was probably the most reliable point for the determination of the systolic pressure, all the systolic readings in this paper were taken at this point, and each represents the mean of three observations. This was usually some 3 or 4 mm.

Method of recording the venous blood pressure. A wide-bore manometer (Pl. 19), 10 inches in height, funnel-shaped at the top, and having at the lower end a right-angled turn to which a small tap was attached, was used. A large salvarsan needle was connected to the lower end of the manometer by a short length of rubber tubing.

Immediately before use the manometer is filled with a sterile solution of 0·5 per cent. of sodium citrate in normal saline. The subject is recumbent, the head being low. A well-marked median basilic vein is chosen, and then, with due aseptic precautions, the needle is plunged into the vein in the direction of the blood-stream. The tap at the lower end of the manometer is then opened, and in a short time the solution falls to a steady level. This level records the mean pressure in the venous system at the point chosen, the zero mark being the lower end of the manometer, which must be at the same level as the point of puncture of the vein. Clotting does not occur, and the oscillations of the column due to respiration are plainly visible. It is obvious that this method does not lend itself to frequent observations on the same subject.

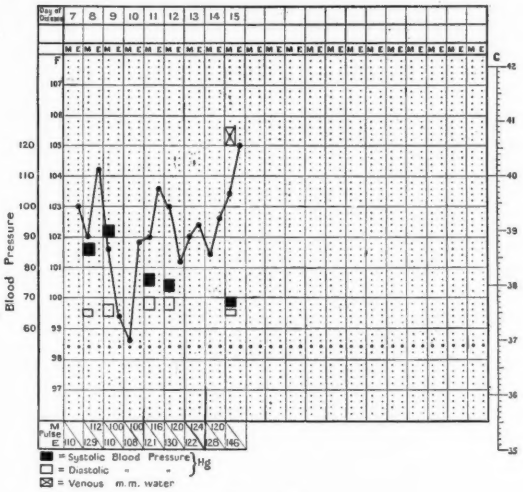
A series of observations upon the arterial and venous pressures in healthy soldiers showed arterial systolic pressures of from 115 to 125 mm. Hg, diastolic of from 35 to 65 mm. Hg, and venous pressure of 40 to 60 mm. of water. A few actual readings are appended.

	Systolic.	Diastolic.	Venous.	Pulse-rate.
No. 1, aged 25	120	30	65	70
„ 2, „ 23	115	45	61·5	68
„ 3, „ 25	127	38	60·75	65
„ 4, „ 25	125	60	45	75

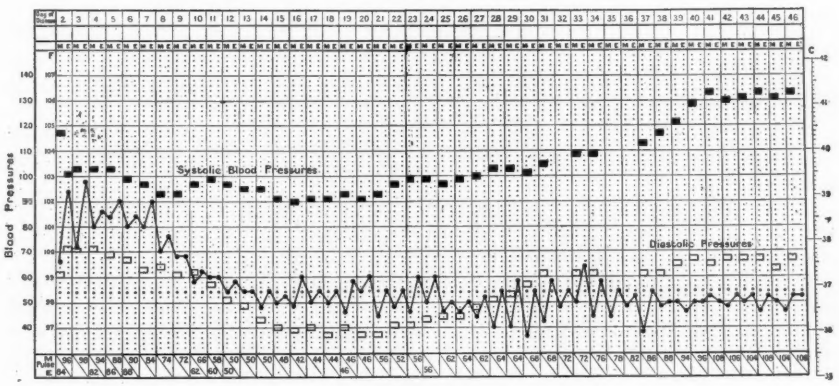
Arterial and venous pressures upon cases of the enteric group. Case I. Typhoid, died on 15th day of disease; the lesions characteristic of the disease were found at the autopsy; the bacillus typhosus was recovered from the spleen and the bile.

The arterial systolic pressure is excessively low and shows a fall from about 90 mm. on the 8th and 9th days of his disease to only 70 mm. Hg on the day of death. The arterial diastolic pressures are seen to lie between 65 and 70 mm. Hg. A single reading only of the venous pressure was taken on the last day and it was found to be 122 mm. of water.

Comment. Low systolic pressures were constantly observed in severe cases and a very close approximation of the systolic to the diastolic pressures in the fatal cases. The high venous reading is noteworthy.



CASE I.

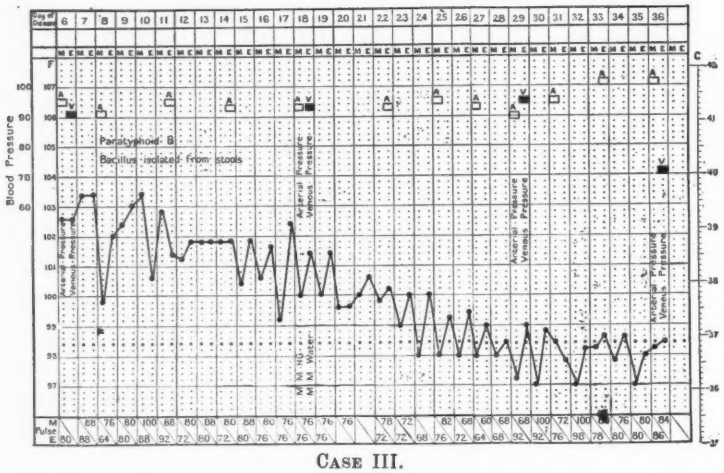


CASE II.

Case II. Paratyphoid A, moderate severity; the bacillus paratyphosus A was identified in the blood.

Observations were taken upon the arterial pressures at fixed hours daily throughout the disease. A study of the curve of the systolic pressures shows a rapid fall during the early days of the disease, a constantly low level during

the 2nd and 3rd weeks, and thereafter a gradual rise is noted, until the end of the 5th week. In the 6th week a more abrupt rise occurs, the pressures reaching 130 mm. Hg. Judging from those cases in which records were taken from the early days of the disease such a curve appeared to be a constant phenomenon in each member of the enteric group. The rapid fall, the low pressure maintained during the 2nd and 3rd weeks, and the gradual return to the normal were seen in all these cases. Frequently, as in the case under discussion, a height considerably above the normal was reached and kept for a few weeks before the pressure settled down. The diastolic curve shows close approximation to the systolic curve from the 3rd to the 10th day, the difference being about 30 mm. Hg. Thereafter the gap is seen to widen until a difference of 60 mm. is constantly recorded during convalescence. This approximation of the systolic and diastolic curves was always seen whilst the patient was acutely ill, and is indicative of cardio-vascular embarrassment.



CASE III.

Case III. Paratyphoid B. The bacillus paratyphosus B was recovered from the urine. The systolic pressures were frequently taken; in addition observations upon the venous pressures were made on four occasions—on the 6th, 18th, 29th, and 37th days.

A study of the systolic curve shows the characteristic low pressures during the acute stages of the illness, also the beginning of the return to the normal on the 33rd day.

The venous pressure was taken on the 6th, 18th, and 29th days, and was found to be between 90 and 96 mm. of water; that is, to a height only slightly above that witnessed in healthy controls.

Comment. It thus becomes evident that when the arterial pressure falls the venous pressure rises, and vice versa when the arterial pressure rises the venous pressure falls; that is, during the acute stages of the disease the reverse of the normal is seen.

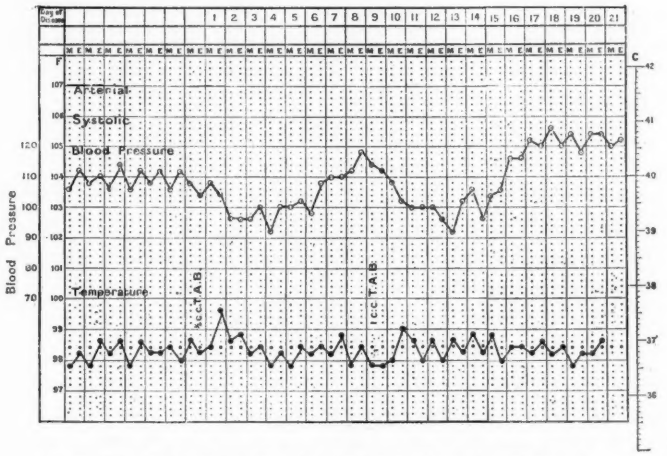
The arterial and venous pressures in cases of thrombosis occurring in cases of the enteric group. A series of observations were made upon the arterial and venous pressures in cases of the enteric group in which thrombosis was present. Exceptionally high readings were found in all such cases, and the pressure was observed to fall with the subsidence of the condition.

	Day of Disease.		Arterial.	Venous.	Pulse-rate.	Site of Thrombosis.
1.	40th.	Typhoid	110 mm. Hg	90 mm. water	119	R. and L. iliacs
	45th.	,,	124 ,, ,,	33 ,,	124	
2.	25th.	,,	120 ,, ,,	110 ,,		L. femoral
	29th.	,,	125 ,, ,,	90 ,,		
3.	44th.	Para. B	97 ,, ,,	105 ,,		,,
	50th.	,,	103 ,, ,,	76 ,,		

The possibility that a high venous pressure is a contributory factor to the causation of thrombosis occurs.

Observations upon the arterial blood pressure before and during the first few weeks after inoculation against the enteric fevers.

Case IV. Some difficulty was experienced in finding a subject for this observation as uninoculated men are rare in the Army. A healthy uninoculated man was eventually discovered: he was shown bacteriologically and serologically to be free from present or the results of past infection by a member of the enteric group of organisms. He was put to bed for a week prior to inoculation, during which time careful morning and evening records were taken of the systolic blood pressure, which was found to vary between 107 and 113 mm. Hg. In addition his blood, stools, and urine were repeatedly examined for organisms of the enteric group.



CASE IV. Patient detained in Bed throughout the Observations.

Inoculation was then performed with ½ c.c. of T.A.B. vaccine, and nine days after the initial dose of vaccine a second dose of 1 c.c. was given; a very mild reaction followed each inoculation. The subject was unconscious of any disability. Observations of the blood pressure were continued for three weeks after the first inoculation.

A study of the curve immediately after the first injection shows a fall of 20 mm. during the first four days, followed by a rise, the curve attaining a height of 118 mm. by the 8th day. The second injection was given on the 9th day and was followed by a fall for the next four days, after which a rise took place to a height of 125 mm. on the 18th day. Thereafter the pressure fell until 120 mm. Hg was reached by the 22nd day, when the observations were concluded.

The above observations have been repeated on several occasions with similar results.

It would thus seem that inoculation against the enteric group produces a temporary fall in the arterial pressure similar to that seen during an infection by each or any member of the group. Thus we are led to conclude that not only are the living organisms capable of affecting the blood pressure, but that a sterile emulsion of the same, such as is used in inoculation, will also bring about a similar result: therefore this effect must be produced by some toxins in the bacilli.

The arterial pressure in man is dependent upon the following factors: (1) the systole of the left ventricle; (2) the elastic recoil of the arteries; the viscosity of the blood may also be a factor.

In regard to the first factor, in another paper [1] I have endeavoured to show that the toxins of enteric fevers have an inhibitory effect upon the neuromuscular elements of the vagus nerve in the heart, causing a loss in systolic efficiency, and that similar results follow inoculation against these fevers. Such an action on the part of the toxic products in question might, and probably does, serve as one factor in the lowering of systolic arterial pressure and other phenomena described in the above cases.

With a view to ascertaining the part played by the second factor—the elastic recoil of the arteries—observations were taken upon the action in enteric patients of certain drugs known to act upon healthy arterioles and so modify the arterial pressure in the normal subjects.

The reaction of the arterial and venous pressures to amyl nitrite. Amyl nitrite is said to dilate the arterioles and veins, causing a greatly increased heart rate and a considerable fall in blood pressure. The action of this drug was studied in healthy orderlies in the following manner: The pulse-rates were controlled by a polygraph with time-marker attached. One observer recorded the systolic pressures as frequently as possible, the time of each observation being instantly marked on the roll of the polygraph. A second observer watched the venous manometer.

The subject breathed through a short wide rubber tube with a glass mouthpiece attached; into the rubber tube 1½ mm. of amyl nitrite were sprayed from a scent-bottle during a single inspiration. The various observations were made before, during, and for a few minutes after inspiration of the drug. The subjoined chart shows the changes usually recorded.

The pulse is seen to rise from a steady 75 to 130 per minute, then to fall more slowly.

The arterial pressure falls from 116 to 96 mm. Hg, the low pressure occurring with the maximum acceleration of the heart; thereafter the pressure rises and more gradually regains the normal.

The venous pressure rises gradually from 60 to 82 mm. of water, and then

[1] *A Report upon the Use of Atropine as a Diagnostic Agent in Typhoid Infections*, published by the Medical Research Committee. By Captain H. Fairley Marris, M.D., R.A.M.C. August 3, 1917.

falls, the equilibrium of both arterial and venous pressures being restored some five minutes after the inhalation of the drug.

The subject became flushed and felt a throbbing in the head, and the pulse became dicrotic in character.

Similar observations were made upon cases of the typhoid group, during the height of the disease, with fever, low arterial blood pressure, and dicrotic pulse. In each case the rise in pulse-rate was negligible, the fall in systolic pressure was small, while no change was witnessed in the venous pressure.

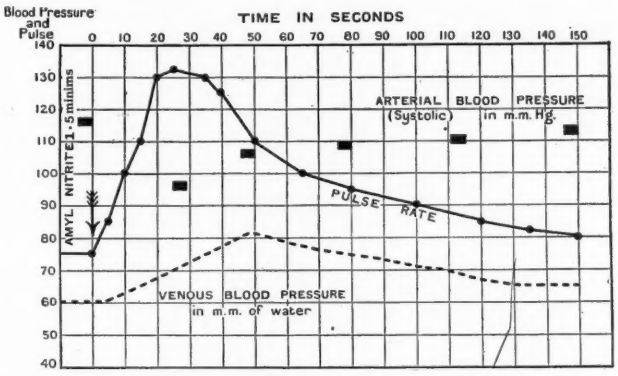


CHART A. Effect of Amyl Nitrite upon Arterial and Venous Pressure in Healthy Man.

Comment. The phenomena produced by amyl nitrite were already present, the rapid pulse alone being wanting. That this should be present was not to be expected, since, as I have shown in the paper already referred to, the toxins of the typhoid group of organisms act upon the pacemaker, or the vagal mechanism of the heart, in such manner as to produce the relatively slow rate which is so characteristic of these infections.

We thus see that the arterial and venous pressures in the typhoid group are scarcely influenced by the exhibition of amyl nitrite.

The reaction of the arterial and venous pressures to adrenalin. It was then decided to investigate the action of adrenalin in these conditions. Adrenalin is said to accelerate the heart rate, raise the arterial blood pressure, cause blanching of the skin and dilatation of the pupils, by acting upon the neuro-muscular endings of the sympathetic nervous system. The effect upon healthy orderlies was studied, and it was found that a dose of 0·25 minim of a 1/1000 solution of adrenalin in 5 minims of normal saline produced a reaction of the type shown in the accompanying chart (see chart B).

The pulse-rate rises from a steady 88 to 103 per min., then falls to 65 per min., during which time the pulse waves are seen to be of greater amplitude.[2] The systolic pressure rises from 117 mm. Hg to 143 mm. Hg, then falls,

[2] The primary quickening is due to the direct action of the drug upon the cardiac sympathetic nerves; the secondary slowing to the vagal reflex.

at first abruptly, then more slowly, reaching the base line some 3½ minutes after the injection. The venous pressure falls from 66 to 50 mm. of water, then gradually returns to its former level.

The subject became blanched, the pupils dilated; and he was conscious of the slow forcible heart-beats during that period when the heart was observed to be abnormally slow.

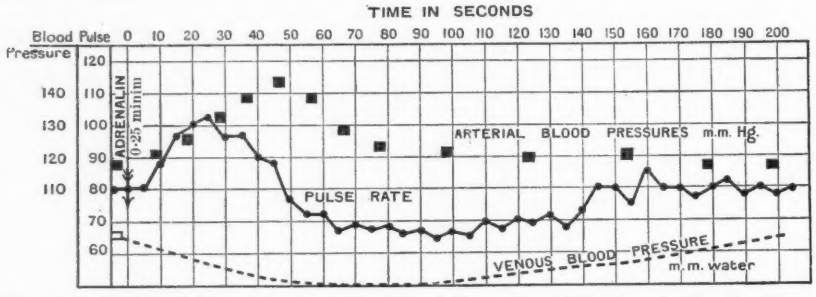


CHART B. Effect of Adrenalin upon Arterial and Venous Blood Pressure in Healthy Man.

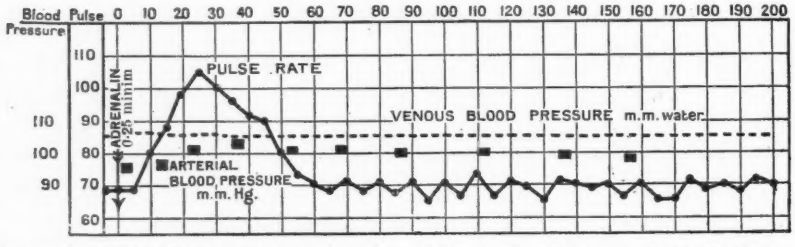


CHART C. Effect of Adrenalin upon Arterial and Venous Blood Pressure in Typhoid Fever.

When a similar dose was administered, at the height of the malady, to a patient suffering from an enteric group infection with high fever, slow and dicrotic pulse, curves as in the subjoined chart were recorded.

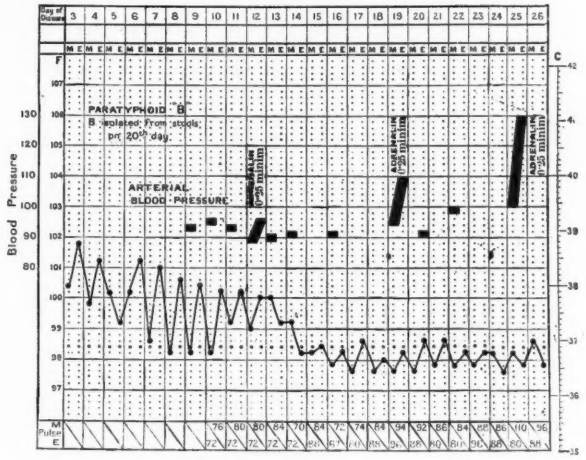
The pulse-rate is seen to rise as in health, then a fall is witnessed, but no abnormal slowing of the heart takes place; the original pulse-rate is soon reached and there remains; the systolic pressure rises some 6 mm. of Hg only and then slowly reverts to the initial level; the venous pressure shows no change. This peculiar reaction of the blood pressure to adrenalin was then studied on different days of the disease, and the effects witnessed in a case of paratyphoid B are recorded below.

Case V. A mild case of paratyphoid fever; the bacillus was isolated from the stools. The blood pressure is low throughout. On the 12th day the adrenalin causes a rise from 88 to 96 mm. Hg, on the 19th day from 95 to 110, on the 25th day the pressure rises from 100 to 130 mm. Hg.

Thus we see that during some period of an enteric infection the blood pressure fails to respond to the drug adrenalin to the same degree as in health, but as convalescence is approached a return to the normal is seen.

Comment. Reference to the pulse-rate in both Chart C and Case V shows a normal acceleration of the pulse-rate after the administration of adrenalin.

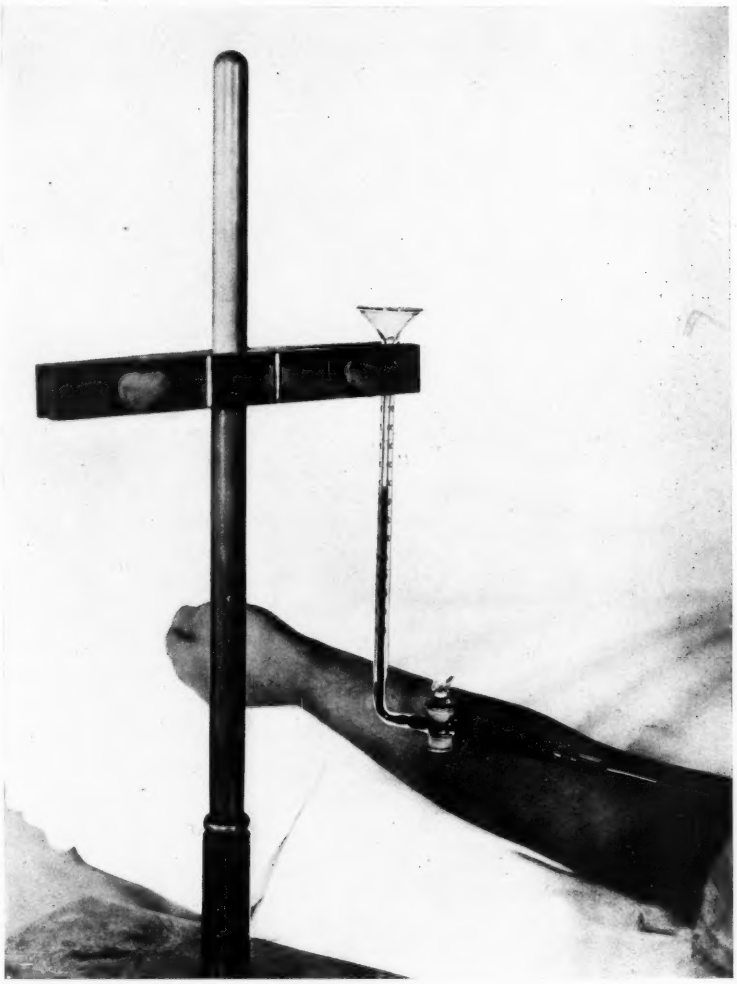
The subsequent slowing witnessed in the case of the healthy control is, however, absent, and that this should be the case was to be expected as the vagus is concerned in the production of this phenomenon. That the primary quickening takes place is, however, a clear indication that the sympathetic nervous mechanism of the heart is in the normal working order. It must be clearly noted, however, that though the response of the pulse approximates the normal, that of the blood pressure is far from so doing. Reference to the charts shows that in the enteric cases the rise of blood pressure after the administration of adrenalin was only some 6 to 8 mm. Hg, instead of 30 to 40 mm. shown by normal subjects.



CASE V.

The indications then are that, although the response of the heart to sympathetic stimulation is normal, that of the arterioles is by no means so.

This leads us to the conclusion that the sympathetic nervous system itself is undamaged, and the failure of the vascular musculature to respond to the secretion of the suprarenal gland at the height of an enteric infection must be explained by the action of the bacterial products either upon the muscles themselves or upon the myoneural elements of the walls of the vessels.



Manometer for recording venous blood pressure directly ; flavine has been added to impart colour to the citrate solution for reproduction.
(Made by Hawksley, London.)



DYSENTERY IN THE MEDITERRANEAN EXPEDITIONARY FORCE

(A Reply to G. B. Bartlett)

By PHILIP BAHR and J. GRAHAM WILLMORE

With Plates 20 and 21

Having entertained for many years before the outbreak of this war very definite views on the aetiology of the two main forms of dysentery, the epidemic or bacillary, and the endemic or amoebic, it came to us as an unpleasant surprise to find that we materially differed, in the conclusions we had arrived at, from Captain Bartlett in his paper in this Journal for April, 1917.

Appearing as it does from one who is so well known to us as a leading pathologist, and to whose work and teaching we are in so many ways indebted, the paper was bound to attract a considerable amount of attention and respect, and it is in this spirit, with no little admiration for the manner in which his pathological examinations have been carried out, that we have studied the paper.

The main object of the paper and the conclusion the author was forced to arrive at, as the result of his many post-mortem examinations, is to show that the epidemic of dysentery which decimated our troops during the whole of the period June, 1915, to January, 1916, or even later, was essentially of amoebic origin. With this conclusion we are in many ways in disagreement. The subject is one which abounds with difficulties, and on these we hope to be able to shed some light.

Our object in writing this paper as a criticism of Captain Bartlett's work springs from a sincere conviction that, if his conclusions are accepted *in toto*, we must regard the dysenteries of all the war zones as being essentially of amoebic origin, and altogether disregard the bacillary factor.

The bedrock on which successful treatment must be founded is prompt and accurate differential diagnosis, and in this respect there are no two diseases in which this should be done more promptly and surely than in the dysenteries, for we have in our hands such specific and well-tested remedies which differ fundamentally in each case.

[Q. J. M., July, 1918.]

Under the conditions of active service it is impossible to banish dysentery altogether: on the other hand, research has provided us with such well-tried remedies in the form of emetine and antitoxin—specific for each of the two great varieties of dysentery—that it is possible to control and reduce to a minimum the military wastage attendant upon its ravages. The attainment of this desideratum entails the intelligent application of these specifics, not to mention the possibility of successful prophylactic inoculation; these are dependent upon prompt and accurate differential diagnosis and a just appreciation of the aetiological factors concerned.

Fully appreciating Captain Bartlett's knowledge of cytology in particular, it is with some diffidence that we venture to express our opinion that in this matter of differentiation he is at fault.

In justification of this attitude we would urge that Captain Bartlett has never, to our knowledge, worked in hot countries, where alone can epidemics of dysentery on a large scale be studied at first hand. It is only by years of patient study in the field, the wards, the laboratory, the mortuary, in hot countries where dysentery is rife, that even a working knowledge of this most difficult subject can be attained.

On the other hand, it has been our fortune to go through such a mill; by reason of it, and the isolation incurred thereby, our methods are doubtless more primitive than those in vogue at the London Hospital; but we submit that this disadvantage, the bugbear of all tropical workers, is more than counterbalanced by the added gain of abundant fresh material, clinical, bacteriological, and pathological. To this must be added a lively appreciation of the difficulties encountered, and particularly of those presented by the varied protozoal fauna of the intestines in hot countries.

After this preliminary statement we propose to examine Captain Bartlett's most interesting and laborious paper in some detail.

With regard to the section on technique, the only points upon which we venture to pass any remarks are, firstly, his choice of Weigert's iron-haematoxylin as his basic stain for amoebae. The greater rapidity of this stain does not, in our experience at least, make up for the loss of the sharp differentiation of amoebic nuclear structure which is given by Heidenhain's iron-alum-haematoxylin. Secondly, his statement that cytological methods have been, and are being, neglected in the investigation of the pathology of dysentery. We would refer him to the report on dysentery in Fiji (1), published in 1912 by P. H. B., to a paper by Willmore and Shearman (2), and to the previously published work of Dutcher (3) and Jürgens (4).

Again, Captain Bartlett makes no mention of the bacteriological technique employed in the examination of his cases, except to say that this investigation was very incomplete; yet he considers these admittedly incomplete investigations as sufficient grounds for excluding the existence of primary specific bacillary dysentery. Even in cases where the post-mortem findings were indicative of this condition, it is dismissed as inflammation secondary to hypo-

thetical amoebiasis in which amoebae could not be detected, or the lesions characteristic of amoebic ulceration were obscured by 'diphtheroid inflammation' (pp. 215 and 223).

How incomplete the bacteriological investigations of Captain Bartlett's series of cases must have been is evidenced by the fact that in not a single instance was he successful in isolating a dysentery bacillus; this in spite of the fact that on p. 223 in the summary of sixty-one autopsies no less than five are classified as revealing 'pure bacillary type of inflammation' and eight as 'bacillary type of inflammation obscuring amoebic lesions'.

We would emphasize that during the same period that Captain Bartlett and his co-workers were meeting with such consistently negative results, P. H. B. in Mudros (working in the laboratory of Lieut.-Col. Martin, F.R.S.), and J. G. W. in a general hospital, Alexandria, were obtaining positive bacillary findings sometimes in more than 70 per cent. of all blood and mucus stools examined (J. G. W. 77 per cent. in November and 90 per cent. in December, 1915) (5, 6, 7). Our cultures were identified by the usual agglutination and sugar reactions. Subsequently we have been continually engaged in Egypt in the diagnosis of the dysenteries. As an explanation of the contradictory results, we venture to put forward the following points:

As one of us pointed out at the time, the particular brand of peptone supplied to laboratories by the Army Medical Stores was quite unsuitable for the isolation of *B. dysenteriae*. Stock cultures only, which had become habituated to saprophytic conditions of life, would grow on it.

This was recognized at once by Colonel Martin and one of us independently. One of us (J. G. W.) prepared two series of control MacConkey plates, one with the army peptone, and the other with Chapoteaut's peptone, which were inoculated in parallel series with fresh dysenteric material. The result of this experiment was to demonstrate, in the most convincing fashion, the inhibitory action of that particular brand of peptone on *first* cultures of *B. dysenteriae*.

In consequence, Colonel Healy, A.M.S. (O.C. a general hospital), at once arranged for a supply of Chapoteaut's peptone for use in his laboratory.

It was not until the early spring of 1916 that this fact was recognized generally. No more of the old peptone was issued, and immediately the disparity in findings between the different laboratories became less. The majority of bacteriologists, in the early part of the campaign, had had little or no previous experience of epidemics of bacillary dysentery; in consequence, they did not appreciate the importance of the manner in which plates should be sown with dysenteric material. Attention to the following details makes all the difference between success and failure:

(*a*) When dealing with faeces—the stool must be examined freshly passed—one of us (P. H. B.) has recently tried the effect of taking cultures, at intervals, from the same stools, in white enamelled iron bed-pans, with well-fitting lids, left lying in a warm place. He has found that, whereas the first plates gave almost

pure cultures of *B. dysenteriae* from plates sown, even at the end of eight hours not a single colony could be recovered.

Moreover, it is not generally appreciated that the specific bacilli are excreted in large numbers in the stools during the early stages of the disease, and that in a rapidly convalescing case they may be irrecoverable from the dejecta, as we have recently experienced, as soon as four days after this period of maximum predominance, and therefore they would not necessarily be capable of isolation from the stools of patients on reaching Alexandria after their evacuation from Gallipoli some ten days previously. It must also be remembered that the dysentery bacilli are not uniformly distributed in stools consisting of faeces and muco-pus, but they are entangled in the latter.

It follows that any of the methods of emulsification of faeces, or enrichment in broth cultures for varying periods in the incubator, such as are recommended when searching for members of the enterica group, are almost certain to be attended with negative results in dysentery. If the stool consists of faeces and muco-pus, a lump of the latter should be picked out and gently washed clean of faecal matter in a little saline, and then crushed direct into the surface of the medium, after allowing all the fluid possible to drain from it.

If the muco-pus can be obtained clean and free from faecal contamination so much the better. For these reasons we both of us prefer that the bed-pan containing the entire stool be brought to the laboratory when possible, rather than receive a 'faeces tube' sample, the choice of which has usually been relegated to an orderly.

(*b*) The technique to be employed at autopsies is no less important. To rub a platinum loop on the surface of the green necrotic mucous membrane—as we have seen done on more than one occasion—which is always teeming with saprophytes, is futile.

The bowel wall must be well washed in normal saline and then dried; the surface is then lightly seared and superficially incised with a sterile knife (P. H. B.). (An alternative method is to flush a portion of the intestine with tap-water and then swab it carefully dry; the superficial layers of the mucosa are then scraped away with a flamed scalpel (J. G. W.).) Then a large platinum loop is filled with as much of the fluid exuded from the lower layers of the mucosa as it will hold and transferred directly without any intermediate steps on to the surface of the plates. (We prefer MacConkey's medium for this purpose.)

In all our experience, both previous to and during this war, we have never succeeded in isolating from heart's blood, bile, spleen, or liver, any organism which could be definitely excluded as being due to a terminal or post-mortem invasion by bacteria of the *coli* or putrefactive groups. We have never isolated a dysentery bacillus anywhere but from the bowel wall; *per contra*, it has fallen to the lot of us to isolate not infrequently, but only amongst debilitated orientals, *Bacillus coli* from pyaemic abscesses in the renal cortex.

With regard to the serological investigations Captain Bartlett admits these also to have been incomplete (p. 239), yet he appears to have attached diagnostic importance to them, and particularly to negative agglutination results with the serum of fatal cases.

In regard to this we would refer Captain Bartlett to a previously published work of ours (8), in which we have drawn attention to the fact that agglutinins are commonly absent from the blood of fatal cases of dysentery proved to be of bacillary origin by isolation of the specific bacteria from stools during life and from the mucous membrane of the colon at autopsy.

In any case the diagnosis of dysentery by agglutination reaction with the patient's serum may with truth be said to be inconstant and inconclusive in general; in addition, the sera of normal individuals may agglutinate the bacillus (9), (10), (11), (12), (13), (14).

Amoebae and refractile cells. Let us now consider the section of Captain Bartlett's paper dealing with pathogenic amoebae and refractile cells and their recognition. On p. 198 he describes the nucleus of an *Entamoeba histolytica* stained with Weigert's iron-haematoxylin, as a small sharply defined ring, the scanty chromatin of which is confined to the rim with the occasional exception of a nodule of chromatin in the centre of the nucleus.

How does this description, admitted by everybody to be accurate, tally with Plate 26, Figs. 4 and 8? Be it remarked that both these figures are drawn from sections of a colon which at autopsy revealed the lesions of 'bacillary inflammation' (Table II, No. 46, pp. 210 and 231). Further, the patient had died after receiving more than 10 grains of emetine hypodermically, and 'amoebae had persisted in the faeces in spite of treatment'. He had developed dysentery in hospital when convalescent from enteric and died after three months' illness.

With few exceptions Captain Bartlett's figures of the pathogenic amoebae are nothing like so convincing to an impartial observer as those already published by Wenyon and O'Connor (16), and by the former (15), (cf. Manson's *Tropical Diseases*, 1917), Hartmann (17), James (18) in the Philippines, Walker and Sellards (19) in Panama, Werner (20) and Viereck (21) in Africa, and Kuenen (22) in the Dutch East Indies. To be quite candid the entamoebae portrayed in Plate 26, Figs. 2 and 3, very much resemble specimens of the non-pathogenic *Entamoeba coli* which we have obtained from stools of convalescing cases of bacillary dysentery quite untreated by emetine.

We have consistently followed the rule that *Entamoeba histolytica* occurs in the blood and mucus and contains ingested red cells in those cases in which it is the cause of the dysentery from which the patient is suffering; on the other hand, one must bear in mind that *Entamoeba coli* is an extremely common parasite in the Near East, and occurs commonly in the stools of convalescent bacillary dysenteries when treated with saline aperients. Under these conditions this parasite is very active, is found only in the faeces, not in the blood and mucus, and never contains red cells.

We therefore submit that his figures of 'proven amoebiasis' are, to our

minds, untrustworthy, and in combination with his inadequate bacteriological investigation are apt to convey a wholly wrong impression of the prevalence of amoebic dysentery in the Mediterranean Expeditionary Force. To our minds far greater importance should have been attached to the bacillary form as a cause of invaliding and death.

Refractile cells. We approach the question of *refractile cells* with more diffidence, recognizing as we do the author's position in cytology; with three of his statements, however, we are in complete disagreement. In the first place, he emphasizes (p. 199) that, in examining stained films, he neglects all cells with fragmented nuclei. Why? Surely refragmentation, karyorrhexis and pyknosis, is a phase of nuclear degeneration, and we are not dealing with normal histology when examining dysenteric stools and lesions. Again, what other construction can be placed on Plate 27, Fig. 17 than that the nucleus in the process of chromatolysis has suffered fragmentation?

This statement of Captain Bartlett's must surely again have slipped his memory when offering his readers Plate 28, Fig. 23, which he describes as a macrophage, 'the nucleus of which has degenerated; the two chromatin masses in its cytoplasm possibly represent the remains of its nucleus'.

The second statement which we are unable to accept is that these refractile cells are not human body cells (p. 201), but possibly represent an intermediate stage in the life-history of the amoeba.

This assumption, as far as we can gather from a most careful perusal of Captain Bartlett's paper, appears to rest upon no firmer evidence than the crescentic arrangement of the chromatin around the rim of the nucleus and the remark of a candid protozoologist (p. 206), namely, 'We know the amoeba and we know the cyst, but we don't know for certain what happens on either side of either of them'.

With regard to the former, we can definitely state that while ringing of the nucleus in these cells is almost constant, the fusiform contour of the sectors forming the ring is non-specific and can often be seen in the nuclei of polymorphonuclear leucocytes in faecal films of bacillary dysentery, and it is by no means invariable in refractile cells; see Plate 27, Fig. 13.

As far as the candid protozoologist is concerned, we can only say that both he and Captain Bartlett seem to be unaware of the very important and convincing work of Lieut.-Col. Wenyon, R.A.M.C. (23), and Drs. Penfold, Woodcock, and Drew on the life-history of the pathogenic amoebae (24).

Surely these observers have studied the periods between the large vegetative form and the cyst, and between the cyst and the vegetative form, sufficiently thoroughly to controvert the criticism that protozoologists know nothing of 'what happens on either side of either of them'. At all events their results are far from confirming Captain Bartlett's assumption.

The third criticism which we have to offer concerns the origin of these cells and the suggestion (p. 207) that the criteria for diagnosis of amoebiasis be altered to include these refractile cells, or at least, that their presence in the

stools be considered sufficient to warrant a course of emetine treatment. With this suggestion, for reasons to be described later, we must admit we are in direct disagreement.

In the first place, Captain Bartlett offers, as far as we can see, no tangible evidence whatever that these cells are concomitants of vegetative *Entamoebae histolyticae*; on the contrary his description of their persistence in the stools of patients after six days' treatment (pp. 207 and 208) comprising rest in bed, 'no diet' or 'milk diet', and gr. $\frac{1}{2}$ of emetine twice daily, renders his theory all the more untenable. No mention is made whatever of any control cases receiving the same general treatment, but without the emetine. Moreover, we have in our possession numerous slides showing cells morphologically indistinguishable from 'refractile cells' in large numbers which we have obtained from stools of patients in which we could find no trace of any amoebae, and from which we have isolated dysentery bacilli, notably Shiga's bacillus, of classical type in almost pure culture.

In a paper written by one of us (J. G. W.) before seeing Captain Bartlett's communication, these cells are described and their origin discussed; the suggestion is offered that they are all macrophages of endothelial origin, that the peculiar appearance of their nuclei, and to a minor extent of their cytoplasm, is due to and characteristic of bacillary dysentery, and that the degree of chromatolysis observed depends entirely upon the extent to which they have suffered from the specific karyorrhetic influence of the bacillary toxin.

Endothelial macrophages, even with fragmented pyknotic nuclei, are often observed in amoebic stools; but so far from the 'refractile' stage being common in amoebiasis, or in any way associated with it, we consider its presence to any noticeable degree indicative of the stool containing it belonging to the bacillary variety.

We think that this section of Captain Bartlett's paper furnishes further evidence that he was dealing unwittingly with bacillary dysentery, either simple or complicated by coincident amoebiasis.

Again, on p. 201 the author commits himself to the statement that in stained films 'entamoebae and refractile cells have quite definite characteristics which serve to differentiate them from human body cells'. On p. 200 he says that they are not endothelial cells because their nuclei are too small. How does he reconcile these statements with his own illustrations of refractile cells on Plate 27, in which they are figured with nuclei every whit as large as those of the admitted endothelial cells in Fig. 18? Most contradictory of all to his previous arguments is the author's own description of this particular figure, and we therefore quote it in full: 'Clump of large endothelial cells from a blood-vessel. The cells show typical large endothelial cell nuclei which are undergoing chromatolysis. One large cell shows a refractile cell nucleus with fusiform collections of chromatin on the nuclear membrane. Faecal film from a non-fatal case.'

How again does he reconcile this with his statements on p. 207? 'This

fusiform or crescentic condensation of chromatin on the rim of the nucleus is *not* commonly seen in nuclear degenerations . . . these clean-cut crescents are, in my experience at any rate, found only in dysentery and one other disease of unknown aetiology.' (By dysentery we presume that the author refers to amoebiasis.)

That all these cells really are macrophages of endothelial origin is, we submit, proved by a study of Plate 20 illustrating our article. It is taken from a section of a small capillary in the submucosa; the area is outlined in Plate 21 from the same case of the sigmoid of a fatal case of bacillary dysentery from Gallipoli. Shiga's bacillus was isolated in large numbers from underneath the green necrotic false membrane at autopsy.

This section illustrates in an admirable manner the derivation of the phagocytic macrophage cell from the capillary endothelium, in all stages of its evolution from the undoubted endothelial cell with typical nucleus, through its phase of phagocytic activity, to its disintegration into the refractile cell of Captain Bartlett. On the other hand, might these cells not also be young and vigorous endothelial cells swollen up by the purely physical action of osmosis and which have not reached the stage of ingesting red cells?

These cells are well seen first of all in unstained preparations, and resemble amoebae, especially when they contain red cells, to such an extent that they are constantly mistaken for them by beginners. By Achard's method of eosin staining, the dead cells can be differentiated from the living, and by infiltrating the cover-glass preparations with a solution of Sudan III the fatty changes which they have undergone show up admirably.

In permanent films fixed with sublimate-alcohol and stained with 'W' stain, which combines the nuclear effect given by iron-haematoxylin with a Romanowsky picture of the other structures, all phases of this evolution may be demonstrated in the one preparation (of course the fatty changes do not show).

We invite comparison of these cells as seen in the fresh stool with Plate 20, Fig. 2, and also of the cells 3 and 3 *a* in Plate 20 with Captain Bartlett's 20 and 24, Plate 28. (We would emphasize that these plates were drawn before Captain Bartlett's paper was brought to our notice.)

We draw special attention to the text accompanying these plates and to the large number of macrophage cells in the deeper layers of the submucosa in Plate 21.

Some of these cells are obviously of vascular and others of lymphatic origin, as Captain Bartlett describes.

We would point out that Captain Bartlett's failure to find these peculiar cells in other inflammatory foci, such as the nose and the sinuses of lymphatic glands, is not surprising, should the conclusion at which we have arrived be correct; the one by a study of the cellular exudate in the stools, the other by microscopic sections from cases of proven bacillary dysentery; namely, that the peculiar nuclear changes under discussion are stigmata of degeneration peculiar to the action of toxins of dysentery bacillus.

This leads to a consideration of p. 215 and a reference to Plate 34. Here Captain Bartlett has exactly described the same appearance as drawn in Plate 21 of this article. An interesting comparison can be drawn between his plate and one painted by one of us (P. H. B.), Plate 3 in his paper on dysentery in Fiji in 1910, an instance in which verification of the diagnosis was made by isolation of the specific bacillus. There can be little doubt in the mind of an impartial observer that Captain Bartlett was here dealing with a typical bacillary infection.

In section 4 of his paper the author discusses the effect of treatment upon the cytological contents of the stools.

The treatment adopted comprised, *inter alia*, the hypodermic administration of 1 gr. of emetine hydrochloride daily up to 6 or 10 gr. After an interval further short courses were given. In spite of this, in eight out of thirty cases so treated 'a watery purulent diarrhoea' persisted, in which vegetative entamoebae and refractile cells were present after six days.

In three of these they apparently persisted indefinitely, as the author mentions having found them in sections of the gut-wall from a man who died on the eighteenth day.

Now it is our experience, and, we believe, that of most medical men who have had previous experience of dysentery in hot countries (cf. Rogers, *The Dysenteries* (25)), that acute cases of uncomplicated amoebic dysentery never fail to respond, as far as their urgent clinical signs and the presence of vegetative amoebae in the stools are concerned, rapidly and completely to 2 or 3 gr. of emetine at the most. By this we do not mean that the patients have got rid of their infection, but it is certainly contrary to our experience to find 'large vegetative entamoebae' other than *Entamoebae coli* in the stools of any case so treated.

Stools. We cannot pass undiscussed Captain Bartlett's description of the different types of stools, as his findings are entirely opposed to our own experience, and we feel certain that, if Captain Bartlett could see and investigate early cases of dysentery in the field, he would alter his opinion.

The typical stool of an early case of acute bacillary dysentery is, as we have so often insisted, and as is supported by a mass of evidence, composed of gelatinous mucus with a varying amount of blood, according to the severity of the case; in the majority of cases there is no addition of faecal matter.

From stools such as these we frequently obtain a pure culture of dysentery bacilli, and it is only when the necrosis of the mucous membrane has taken place that one obtains a 'watery yellow or greyish faecal fluid with little mucus and very little blood' (p. 204). His group A types (*b*), (*c*), (*d*), (*e*) are, in our opinion, bacillary stools in different stages of the disease; especially is this true of the 'grass-green stools' of type (*d*), the appearance of which, we think, is produced by the shedding of the bile-stained necrotic 'false membrane' from the mucosa of the colon and even the ileum as well, in severe and fatal cases.

In this connexion the statement occurs (p. 237) that 'polyvalent anti-dysenteric serum, prepared in Alexandria from local strains . . . was said to be useful in those cases where a purulent diarrhoea persisted in spite of the cure of amoebiasis by emetine treatment. This was a potent serum ; it agglutinated all my stains of dysenteric bacilli as well as paratyphoid A and B. I do not know how it was prepared. The Lister antiserum was said to be much less efficacious. Opinions as to the value of antiserum treatment varied greatly; the majority of the clinicians placed no reliance on it.' We are happily in a position to shed some light on this.

The serum mentioned was prepared by one of us (J. G. W.) when working under the late Sir Armand Ruffer from 1909 to 1914. The work was then carried on, with J. G. W.'s cultures isolated at El Tor, by M. Piccinini of the bacteriological department of the *Conseil Sanitaire Maritime et Quarantenaire d'Égypte.*

Its effects were, we think, due to the fact that the mannite fermenting type of the bacillus is so commonly the morbific agent in dysentery occurring in this part of the world; special efforts were directed to obtaining antibodies to this bacillus by using, in its preparation, first of all digested bacillary emulsions, and later 'colloidal toxin' prepared by a modification of the late Sydney Rowland's method for isolating a toxic nucleo-albumin from *B. pestis.*

For further details of its preparation and the effect which it had in lowering the mortality at El Tor from 70 per cent. to 10 per cent., we would refer our readers to articles by Ruffer and Willmore, *British Medical Journal*, 1908 and 1910, and Willmore and Savage, *ibid.*, 1913.

Paratyphoid A and B were included for experimental reasons. The fact that the serum was admitted by some to be useful is, to us, further evidence that many of Captain Bartlett's cases, if amoebic at all, were complicated by coincident bacillary infection, and it was from this latter infection they were mainly suffering.

The unfavourable opinion expressed by the majority of his clinicians finds no echo in the article by Captain Fisher, R.A.M.C., in the *Journal of the Royal Army Medical Corps* (26) upon results obtained by him at a general hospital, Alexandria; the discrepancy is probably due to the fact that, to our certain knowledge, the majority of clinicians at that date were administering the serum in doses of 10 and 20 c.c.; the vital importance of giving it in massive doses of 60 to 100 c.c., repeated as often as necessity indicated, was not then appreciated.

Analysis of Captain Bartlett's post-mortem tables leaves us with the impression that in the discussion of his findings he is often arguing *ex hypothesi*, since when he can find no amoebae to support his contention (p. 208) that 'at least 80 per cent. of the clinical dysenteries had amoebiasis', he falls back upon the assumption, entirely unsupported by any positive evidence, that clinical signs and post-mortem appearances, generally admitted to be typical of bacillary dysentery, must be due to what he terms 'secondary inflammation'.

By this it must be distinctly understood that we do not wish to imply

that the excellent plates, Nos. 30, 31, 32, and 33, do not represent typical amoebic lesions, for in our opinion they do.

We have observed amoebic lesions in three cases in Lemnos, and two since in Cairo, treated and untreated by emetine. In both the latter we have found large numbers of amoebae in the submucosa and peritoneal veins in sections, and in one there was a large amoebic hepatic abscess.

We do not deny that typical amoebic dysentery occurred in the Expeditionary Force, and that Captain Bartlett describes many examples of it in his paper, and has thereby considerably enlarged our knowledge of the subject. We admit that it was commonest in the early part of the Dardanelles campaign, but it was never decidedly epidemic, nor could the large amount of morbidity be attributed directly or indirectly thereto.

We have already commented upon the absence of what should have been perhaps the most important side of such an investigation, namely, a thorough bacteriological examination of the intestines of all cases coming to autopsy. Had this been done, we are convinced that among the sixty-one cases tabulated, the diagnosis 'amoebiasis with inflammation' would not have occurred seventeen times without anything to show to what this 'inflammation' was due.

It is not inconceivable that even this proportion (nearly one-third) with signs of bacillary dysentery would have been considerably greater had Captain Bartlett been working nearer to the actual seat of military operations, for in a disease so rapidly fatal as fulminating bacillary dysentery by far the greater proportion would have succumbed before they reached Alexandria, and this, to observers in Lemnos, actually is what seems to have happened, and it therefore follows that bacteriologists in Alexandria never had the opportunity of examining many of the most acute cases either before or after death.

In his summing up of the pathological picture he offers the rather unsatisfactory explanation that this inflammation was secondary to amoebiasis, without adducing very much positive evidence in its favour or informing us as to the nature of the inflammatory infection. Surely this attitude cannot be justified in view of the mass of work of proven value published by a host of workers since the days of Shiga and Flexner in the last century.

Case No. 46 is perhaps the most striking example. The patient developed dysentery in hospital when convalescent from enteric. He was given more than 10 gr. of emetine and died after three months of treatment. In spite of all this, 'amoebae persisted in faeces, there was amoebiasis throughout colon, and a great number of amoebae in sections; inflammation of bacillary type throughout colon'.

No. 20 also developed dysentery when convalescent from enteric. He also had more than 10 gr. of emetine, and at autopsy showed 'amoebiasis throughout the colon and much membranous inflammation of the bacillary dysenteric type'.

No. 19 developed dysentery in hospital—it lasted three weeks, and amoebae were still present (in stools) fourteen days after treatment commenced. Autopsy

revealed 'isolated rounded and transverse ulcers throughout colon; much secondary inflammation in descending colon'.

Captain Bartlett does not seem to recognize that bacillary dysentery, if the patient does not die too soon, produces transverse ulceration as well as membranous inflammation.

When discussing the spleen (p. 229) the author cites three cases as showing marked septic enlargement. In one of these cases (Case 38) the 'amoebic lesions were complicated by severe inflammation'; in another 'they were obscured by a diphtheroid inflammation;' 'in the third there were no amoebic lesions, the case being one of five which *resembled* pure bacillary dysentery'.

It is our experience that the spleen is usually moderately enlarged (7 to 10 oz.), soft, pulpy, and congested in cases of death from acute fulminating bacillary dysentery. The degree of enlargement is directly proportioned to the rapidity with which the patient succumbs, and enlargement is not, as a rule, seen in death from subacute or chronic dysentery, unless, of course, there be some complicating disease such as malaria.

Consequently, we quite fail to see why it should be necessary to invoke the aid of 'marked sepsis' to produce a lesion which can be seen naturally at autopsy, or produced experimentally in animals (J. G. W.), where the subject has died from the effects of dysentery toxins.

In opposition to Part VII of Captain Bartlett's paper, we would offer, as a result of years of clinical and bacteriological experience of this disease, the following general conclusions; but these conclusions are arrived at after the fullest possible investigation of our cases, whereas Captain Bartlett states in paragraph No. 13 that his bacteriological and serological investigations were 'unfortunately very incomplete':

1. That amoebic dysentery always is and always was endemic and sporadic, not epidemic, and requires, as a rule, conditions peculiar to tropical and subtropical countries for its propagation.

2. That the position of bacillary dysentery of specific bacterial origin, as regards its clinical signs, its aetiology, and its pathology, is so well proved that it cannot be relegated to the realm of '*inflammation secondary to amoebiasis*'. Bacillary dysentery is generally a rapidly fatal disease in its acutest form, while the course of an amoebic infection is almost invariably a long one.

3. That all epidemics of dysentery among troops in the field are due to specific dysenteric bacilli; their spread is due mainly to flies, infected food, drink, and it may be to carriers of the bacillus.

4. That bacillary dysentery may be, and often is, responsible for as many casualties as the more concrete dangers of war, and as a cause of disability has taken the place of enteric in former wars.

5. That while cases of amoebic dysentery undoubtedly do occur, either alone or coexistent with some other infection such as enterica or bacillary dysentery, they are not sufficiently numerous to warrant the indiscriminate

injection of emetine into every patient showing signs of diarrhoea or dysentery. Its administration should be restricted to cases of amoebiasis definitely diagnosed by a competent microscopist. Of course ipecacuanha and its derivative emetine, given in suitable doses over a sufficiently long period, we recognize as specifies for amoebic dysentery.

6. That all cases of diarrhoea should be diagnosed 'dysentery' on clinical grounds as soon as the medical officer satisfies himself that they are passing blood and mucus; such a man is a source of infection to his fellows, and he should be removed from them at once without waiting for the pathologist's report.

7. That at least 95 per cent. of the cases now occurring among white troops are of bacillary origin. Consequently all cases should receive at the earliest possible opportunity, independently of a laboratory report, treatment directed against the bacillary and not against the amoebic form of the disease.

The routine administration of the aperient sulphates and, to the serious cases, antitoxin in massive doses, as early as possible, should be adopted in all cases of clinical dysentery in the place of emetine.

Preparations of bismuth and opium as a routine treatment are, in our opinion, definitely contra-indicated in both diseases.

Even if a case turns out not to be bacillary, the serum will do no harm and the salines will do good; on the other hand, emetine, by reason of its depressant properties and by the blind faith it inspires in its administrators, is in our mind harmful to all cases of bacillary dysentery.

We have had the good fortune to see a letter published by Captain Bartlett in the *British Medical Journal* of September 22, 1917, in which he says that 'until the reports are collected and reviewed it would be better to avoid making statements which tend to revive the old controversies of amoebic and bacillary schools'.

We might bring to his notice that the Medical Advisory Committee have published such a report, in which they point out that, as the bacteriological diagnosis of dysentery became more exact, amongst the troops from Gallipoli the proportion of proved bacillary cases rose, while those due to amoebae fell. Their final conclusion (27), (28) is 'that there appears no doubt that in the Egyptian war zone, throughout the year 1916, bacillary dysentery has been by far the predominant variety'.

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DESCRIPTION OF FIGURES.

PLATE 20, FIG. 1. Microscopic section through submucosa of sigmoid colon, same case as Plate 21 from a Gallipoli case (Oct. 1915). Shiga's bacillus isolated in almost pure culture. The section passes through a small capillary in the centre of a small submucous haemorrhage. Stained by Gauducheau's stain (Borel's blue and eosin). 1. Flattened endothelium of capillary wall. 2. Desquamating endothelial cell breaking off from capillary wall with characteristic ring nucleus (? 'refractile cell'). 3. Endothelial cell with ingested red cells (macrophages). 3*a* contains a dark staining body apparently of same nature as seen in fresh cells in stool (see Fig. 2), probably a semi-digested polymorph (compare Fig. 20, Plate 28 in this Journal, April, 1917). 4. Free endothelial cells with ring nuclei corresponding to Fig. 2, B. Compare Plate 27 in this Journal, April, 1917 (? refractile cell'). 4*a*. Endothelial cell with apparent daughter cell corresponding to Fig. 2, C. 5. Polymorphonuclear leucocytes. 6. Lymphocytes. × 700.

FIG. 2. Cells in freshly passed bacillary dysentery stool drawn to same scale (Shiga's bacillus). A. Macrophage cell showing nucleus, ingested red cell, chromatoid bodies, and fat globules. B. 'Refractile cell' with apparent nucleus. C. Macrophage with daughter cell. D. Polymorphonuclear leucocyte. E. Columnar epithelial cell. F. Red cell. × 700.

FIG. 3. Film from a case of amoebic dysentery stained in a similar manner. A. *Entamoeba histolytica* with ingested red cells. B. *Minuta* form. C. Nuclei of disintegrated polymorph leucocyte. D. Nuclei of semi-digested leucocytes. E. Yeast cell. F. *Clostridium butyricum*. G. Eosinophil cell. × 700.

PLATE 21. Transverse section of sigmoid colon from a Gallipoli case from which Shiga's bacillus was isolated post mortem, showing colliquative necrosis of the mucosa and great cellular infiltration of the submucosa. The square outlined indicates the situation from which Plate 20 was drawn. Stained by haematoxylin and eosin. I. Zone of bacillary infiltration. II. Muscularis mucosae. III. Zone of polymorphonuclear cell infiltration and haemorrhages. IV. Zone of oedematous connective tissue. V. Zone of lymphatic spaces with migration of lymphatic and vascular uninucleate and binucleate macrophage cells. VI. Circular muscular coat.

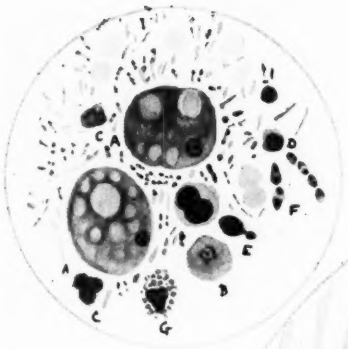


Fig. 3

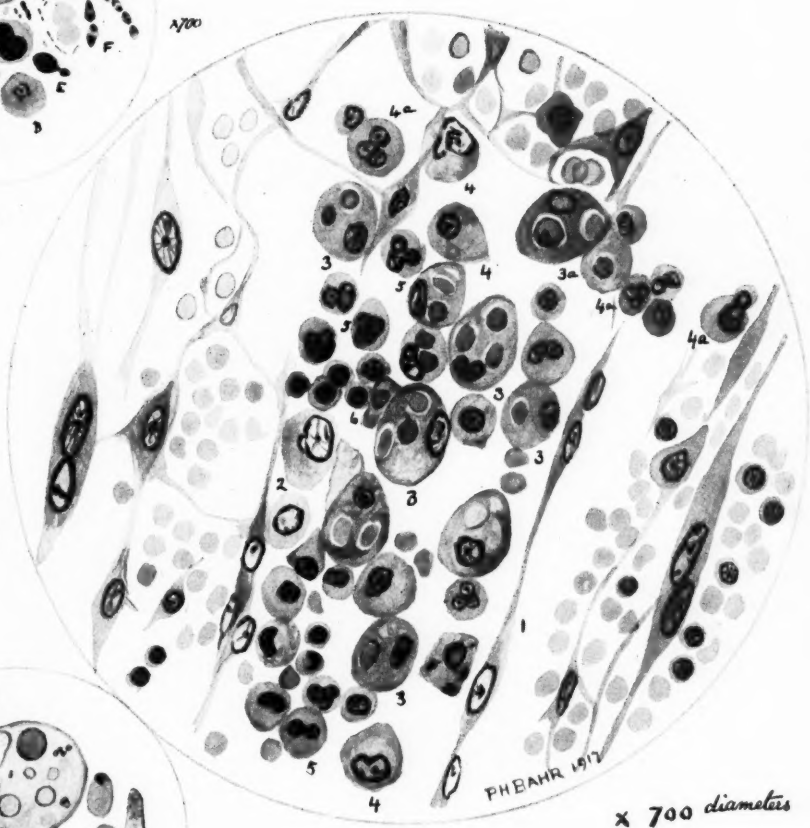


Fig. 1.



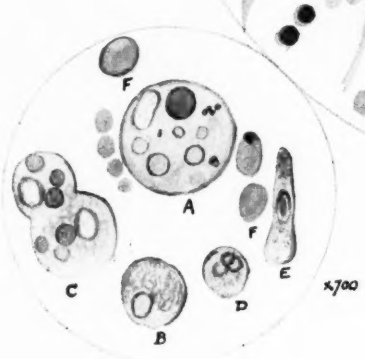
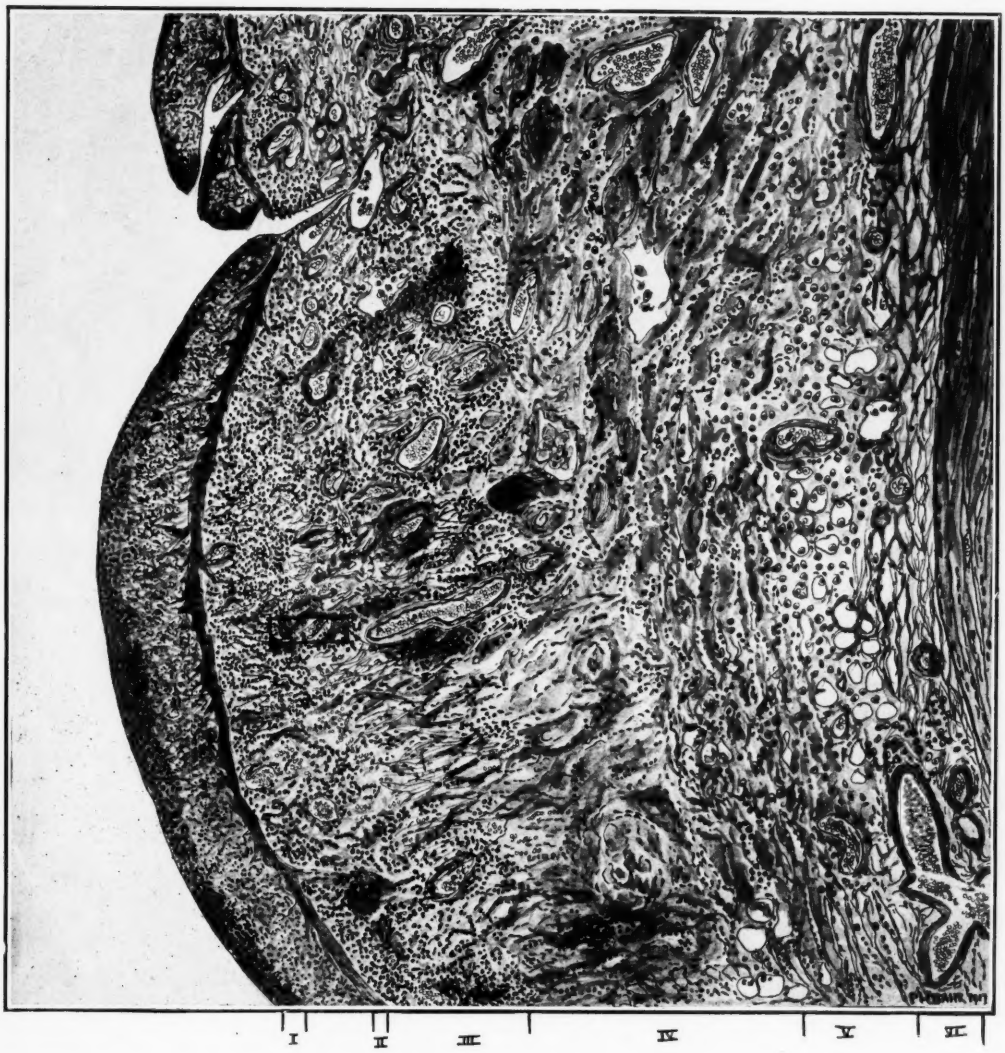


Fig. 2.


I
II
III
IV
V
VI



TRENCH FEVER

A STUDY OF CERTAIN SYMPTOMS

By HORSLEY DRUMMOND

The Eruption.

The characteristic rash of trench fever consists of small erythematous spots, which are usually round, but sometimes of irregular outline, are rosy rather than pink when they first appear, are effaced by pressure, and are level with the surface of the skin. They come out, like the spots of enteric, in successive crops, and like them occur chiefly on the chest and abdomen. They have once or twice been found on the back. But they differ from enteric spots in that they are rather redder than the typical pink enteric spot, have a more indefinite margin, and do not project.[1]

They last from twelve to thirty hours, whereas the enteric spot lasts two or three days. Their number may vary from a single spot to many hundreds. They have been noted in about 30 per cent. of relapsing cases, and in about half that proportion of the irregular forms of trench fever, but this represents much less than the real total. The short duration of the spots, and the pressure of our work, must have caused us to miss many eruptions.

The rash occurs as a rule with fever, and, when the case is of a regular type and relapses can be distinguished, the spots usually appear a few hours before the fever. In a small minority of instances spots are seen on afebrile days. In one or two instances these were days when a relapse of fever was expected but did not appear.

The rash has been seen on the first day, and as late as the thirty-fourth.

In five cases a curious variety of eruption has been noticed. Spots have been found in the zone of supply of one of the spinal nerve roots. Such cases are accompanied with tenderness and recall herpes zoster in their distribution. They are perhaps of different origin from the ordinary rash. It must be added that root zone pain and tenderness have many times occurred without any spots at all.

[1] In France we sometimes see spots in enteric which are both larger and redder than the classical type. They project above the surface.

[Q. J. M., July, 1918.]

Pains.

The pains of trench fever vary greatly in situation, duration, character, and intensity. There is no pain that can be considered distinctive. The shin pains, which have perhaps the best title to be so called, are found, at any rate in France, in enteric, and even in other conditions. Their persistence, sometimes for weeks, is, however, peculiar to trench fever. The commonest sites of pain at the onset are the head, back, and legs.

The most constant of all pains is frontal headache. This is practically invariable at onset, and is often very persistent. Headache is felt in the morning, sometimes for weeks after other pains have disappeared. Pain in the head is sometimes substituted for the word headache by the patient, and probably represents a different kind of pain. It is sometimes felt in other parts of the head, as for instance the occiput or more rarely the vertex.

Occasionally pain and stiffness in the nape of the neck occur at the onset. Several cases have been sent in with the provisional diagnosis of cerebro-spinal fever on this account. In at least two cases this pain was so severe that we did not feel certain of the diagnosis until lumbar puncture had been performed.

Pain in the chest is not infrequent. It is sometimes felt on one side alone, either in the upper or the lower half. In the latter case the left hypochondrium is a far more frequent site than the right, and we have learnt to connect pain in this region with enlargement of the spleen. Occasionally the pain is felt round the lower ribs on both sides.

Some cases have complained of pain in the right iliac fossa very suggestive of appendicitis. In our experience, however, the distinction is not usually difficult. The iliac pain in trench fever is felt when the skin is even lightly touched, and is not increased by deeper pressure. There is not the rigidity characteristic of appendicitis, and there is no tumour to be felt.

Pain in the back, of an aching kind, sometimes referred to the flanks rather than the loins, is the most common of all pains except headache. It lasts almost as long as headache, coming and going for many weeks.

The lower limbs are far more commonly painful than the upper. In order of frequency the shins and thighs are the most often attacked, next the knees and calf-muscles, and then the hips and ankles. Now and again the instep or the sole of the foot is the seat of pain. Shin pains are about as frequent as backache and occur in about two-thirds of the cases.

The arms are much less frequent sites of pain. Almost every part of them has, however, been attacked—shoulders, upper arms, elbows, forearms, and wrists—in our series of cases.

The pains are referred to different structures. The shin pains are referred to the bones themselves, sometimes to definite parts of the bones such as the central part of the bone, or the posterior surface, by the patients.

Pains in the calves, in the thighs, and in the upper arms are referred to the

muscles in those situations, and sometimes to particular muscles such as the deltoid or biceps.

Pains round the knees are referred to places outside the joint. They are not felt to be within the joint itself.

These spontaneous opinions of the patients are usually confirmed by the existence of tenderness. Muscles to which pain is referred, such as the calves or the thigh muscles, are usually tender when squeezed, and there is tenderness round the outside of the knee-joint, especially, it has seemed, at the site of tendinous attachments.

These pains interchange. They will be felt one day in the shin bones, another day in the calves, and a third day in the back. There is no division to be made between cases with bone pains and cases with muscle pains. Nor is there any variety of the disease that can be called shin fever.

There is occasionally superficial tenderness of the skin, as well as the deep tenderness already mentioned. We have seen this over the shins in ill-defined areas, never in small points, and in one case down the inside of the thighs. We have repeatedly searched for an organic foundation such as subcutaneous nodules, but have never found it.

The skin is also occasionally the site of tenderness in areas of the trunk corresponding to the zone supplied by one or perhaps two of the dorsal or lumbar nerves. We have seen instances from the level of the third dorsal to that of the second lumbar. In a few instances these tender zones were the site of an outbreak of the typical spots.

The character of the pain varies. It is sometimes aching, sometimes boring, and sometimes shooting, in the same patient. The boring pain is commonly in the shins, but these may also ache. Shooting pains are generally felt in the length of the limb without any definite reference to structures.

The intensity of the pain varies also. Many patients are kept awake by it, as it is commonly worse at night. A very few patients have had no pain worth mentioning throughout the disease.

An ordinary case will not suffer with pains longer than a fortnight, but in some cases we have seen them last six weeks, and it is known from the observations of others that they may continue for over a year.

Pain and fever often accompany one another, but fever sometimes occurs when a patient says he has no pain and is feeling well, and pain most frequently lasts after fever has subsided.

Ocular Symptoms.

These are—

Conjunctivitis or pink eye.

Soreness in the eyes 'as if there was sand in them', and sometimes definite pain in them or behind them.

Nystagmus.

Occasionally misty vision.

Any one of these symptoms may occur alone. Nystagmus shown on following an object to the right or left is the most characteristic. It may appear at any time in the disease. It has been seen at the onset, and on the other hand has appeared for the first time on the forty-eighth day. Its duration is equally variable. We have seen it almost continuous for forty days. It once persisted, off and on, up to the fifty-eighth day. We have seen it occur on one day alone, but this is uncommon. Usually if a patient has once had it, he shows it again if he remains under observation for three or four weeks. Occasionally when it is on the eve of disappearance it occurs in one direction only, when, that is, the patient looks to the right or left.

Pink eye is perhaps as common. We have seen it in one eye alone, but it is nearly always bilateral. It frequently accompanies nystagmus, but is often seen alone.

Pain in the eyes, and soreness, which are difficult to distinguish, are common. They may occur without any conjunctivitis, and sometimes without any other ocular symptom.

Three of the men complained of misty vision. All of them had nystagmus.

This group of symptoms, whether complete or not, has no regular concomitants. It is seen as often without fever, and without limb pains, as with either. Nystagmus is chiefly known in civil life as the result either of some peculiar use of the eyes (miners), or of some structural malformation in them, or of central nervous disease. In trench fever the last seems excluded by the transient character of the symptom.

Circulatory Changes.

The pulse is nearly always frequent during the bouts of fever (Chart 1, Go.), but there are exceptions (Chart 2, Nl.). As a rule it falls with the temperature to a normal or but slightly raised rate. Frequently, however, at a later date it rises to or above 90 during some part of the day though the temperature remains normal, or if the temperature is a point or two above the normal line the pulse may be much quicker than the slight pyrexia warrants.

In a few cases a rise in the pulse-rate appears to be the only expression of a relapse. These are not included in our cases of tachycardia.

1. TACHYCARDIA. In some cases of tachycardia the increased rate is maintained both morning and evening or varies but little. But in others there is a very marked daily swing, so that the pulse chart looks like that of a violent hectic fever. Sometimes the highest rate is in the evening. The evening rise is often coincident with but sometimes precedes a rise in the temperature, the chart of which may take the appearance of a 'subnormal hectic' (Charts 3, 4, 5, Str., Co., Ba.), but it may occur with a level and subnormal temperature. Occasionally the morning pulse in these cases may be abnormally low, even below 50 per minute.

In some patients, on the other hand, the highest rate of pulse is found in the morning, and the chart looks like a 'reversed hectic' (Charts 6, 7, Cr., Cl.).

The rise in the pulse is sometimes quite sudden, as in Chart 4, or a pulse-rate already above the normal may become suddenly much quicker (Charts 8, 9, Mi., Se.) without any obvious reason.

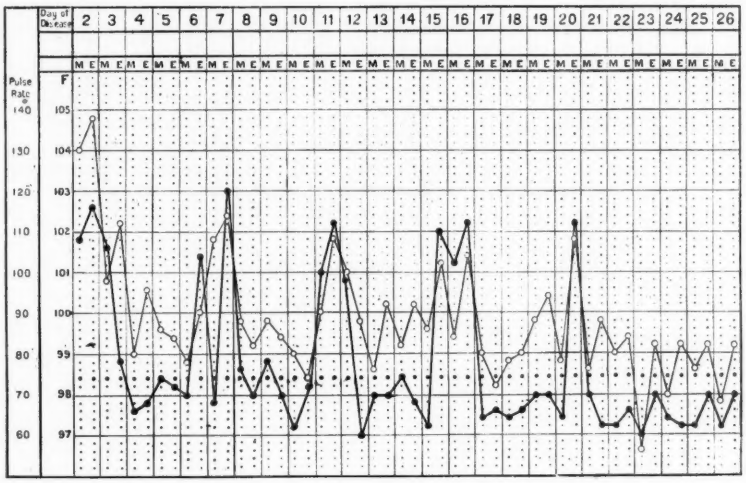


CHART 1. Pte. Go. Age 19. Regular form of pulse-rate rising and falling with temperature.

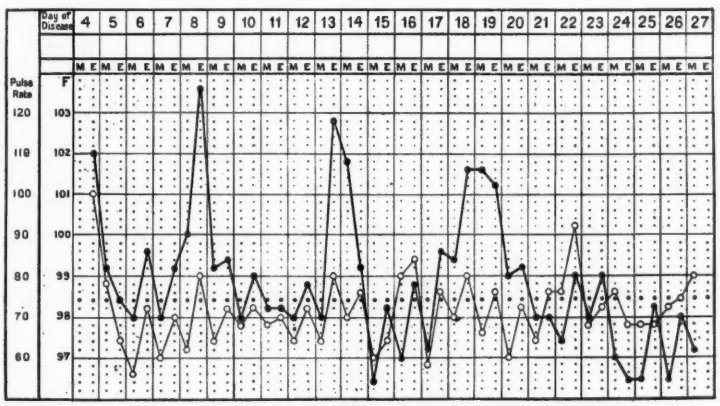


CHART 2. Pte Nl. Age 31. To show exceptional pulse-rate not rising in relapses.

When tested the rate has been much lower during sleep.

In four instances among our patients the pulse has been high from the beginning to the end of their stay in hospital. We suspected that the condition was of old standing.

Many of our patients suffered so little inconvenience that they were dis-

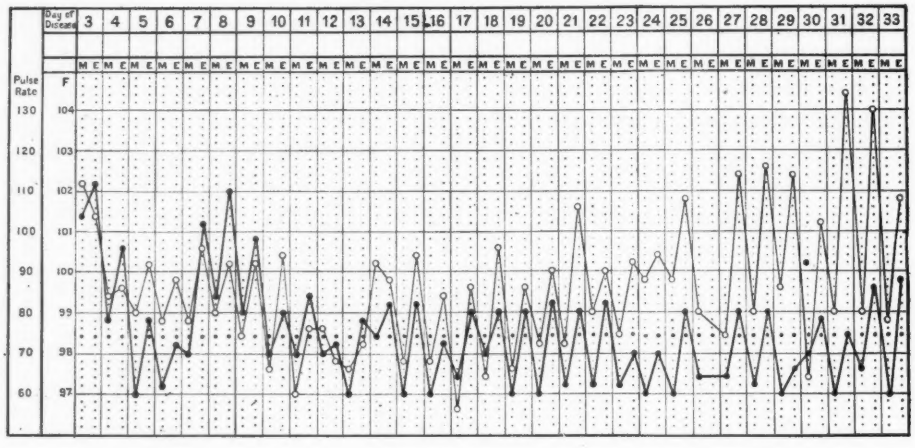


CHART 3. Cpl. Str. Age 30. The first bout ended with the 5th day. A relapse took place on the 7th–9th days. Thereafter the temperature never settled, but developed a very low hectic. The pulse-rate began to accelerate about the 23rd day and became very fast in the evenings. The patient was never out of bed and was evacuated on the 33rd day to the base. The spleen was only palpable on 7th–10th days. There was a good deal of pain up to the 15th, and crops of spots up to the 19th day, but the man felt well on and after the 18th, though he had slight pain and nystagmus on the 21st. The heart reached to ¼ inch beyond the nipple line, and a systolic bruit became audible.

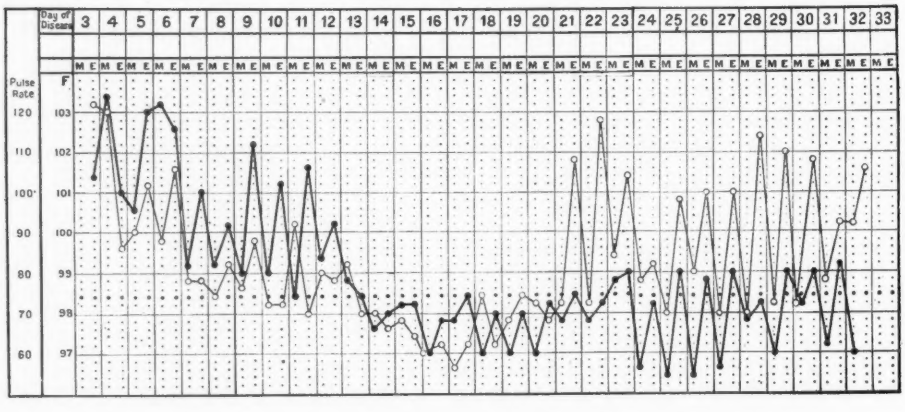


CHART 4. Spr. Co. Age 24. A long fever fell gradually to normal on the 14th day, and the temperature remained subnormal until the 21st day, when it rose to normal and on the 23rd to 99°. Then a period of subnormal hectic fever began. The pulse followed the temperature but began to rise before the temperature, reaching 108 and 118 on the evenings of the 21st and 22nd, though the temperature was not above normal. The patient was in bed up to the 28th day, when he got up for 2 hours, after which he was kept entirely in bed until evacuation on 57th day. The tachycardia, of which the chart shows the beginning, disappeared for no recognizable reason on the 42nd–46th days, but returned as severely as before on the 47th.

charged to duty though the pulse-rate remained between 90 and 100. Others were sent to the base to recover. In a few instances where the men were put on light duty and kept in the hospital the pulse-rate gradually fell to normal within a few weeks.

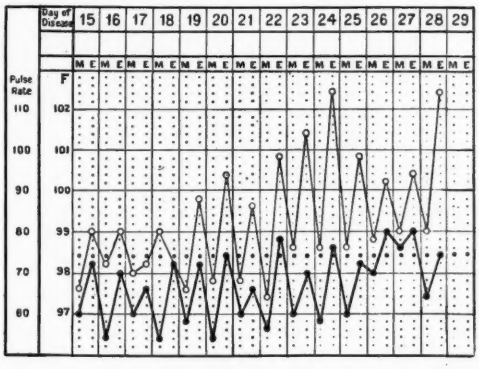


CHART 5. Pte. Ba. Age 21. An irregular relapsing fever fell to normal on the 8th day and the temperature remained of a subnormal hectic type. The pulse never became steady, and on the 19th day began to show a hectic form of chart. The patient got out of bed for the first time on the 18th, and the rise in the pulse-rate is due no doubt to that. He did not suffer from it and was not put to bed again.

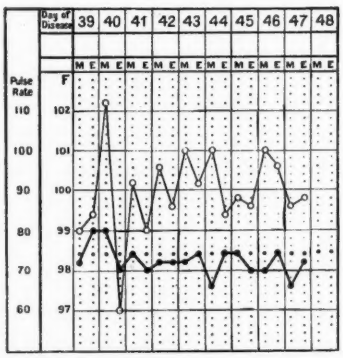


CHART 6. Pte. Cr. Age 28. Showing reversed hectic form of pulse-rate.

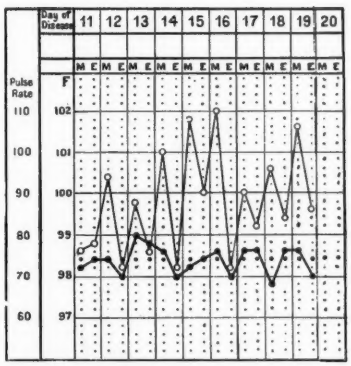


CHART 7. Pte. Cl. Age ? To show reversed hectic form of pulse chart in tachycardia.

There is no doubt that many patients developed tachycardia from being allowed to get up too early (see Chart 9). When we learnt that it was best to keep all but very slight cases in bed for twenty-one days, tachycardia became much rarer. In some cases, however, tachycardia has appeared for the first time, even after the thirtieth day, though the patients had been kept in bed till then, or had been allowed up for a few hours without showing any rise of pulse-rate. A return to bed does not by any means always bring the rate down.

But in many cases tachycardia has begun while the man has been in bed. In most of these the disease was of a severe type. There was prolonged pain, or

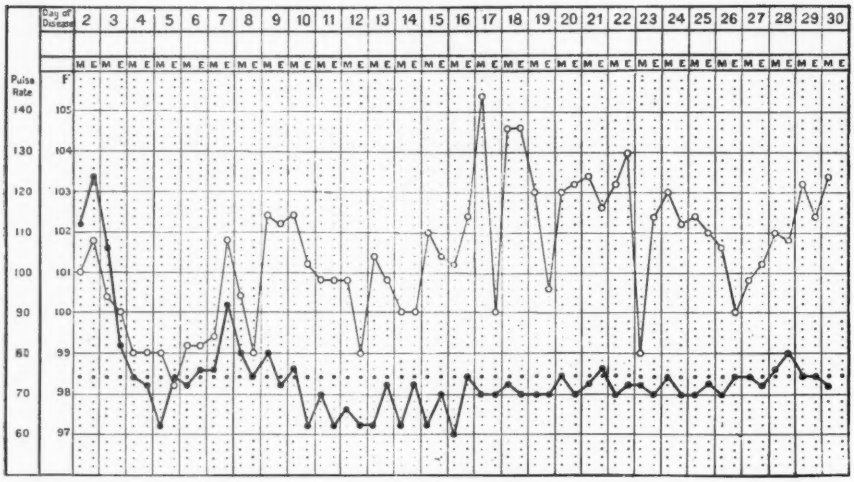


CHART 8. Pte. Mi. Age 29. He was allowed up for a little while on the 7th day, for the afternoon of the 8th, and the whole of the 9th. A relapse happened to come on after he had got up on the 7th. The pulse, after falling with the temperature, rose on the 9th day to 110 and remained high, although he was kept in bed after the 9th day, until the 33rd. During the night of the 16th day he had a sudden attack of breathlessness, and felt, he said, like fainting. The next morning the pulse-rate was over 140 and remained very high for a week. There was nothing known which would account for the attack.

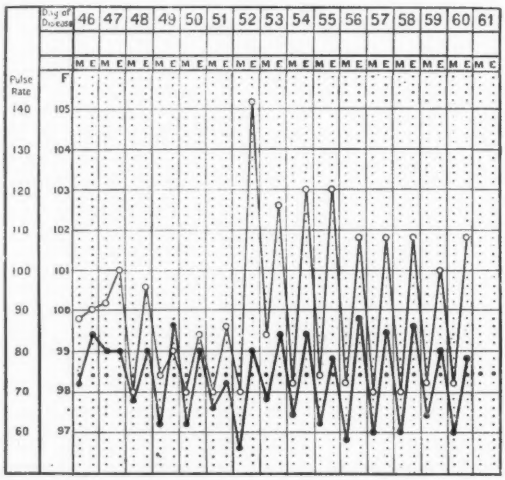


CHART 9. Pte. Se. Age 40. An irregular fever, twice reaching 104°, fell to normal on the 11th day and the pulse fell to 70. On the 12th and following days up to evacuation on the 60th the evening temperature was always raised as is shown in days 46 to 60. The pulse rose to 84 on the 14th and on the 15th to 104 and stayed between 90 and 100 up to the 46th day. The patient was out of bed on days 12–20, 28–34, 40–41, 46–47, and in bed all the rest of the time. On the 52nd day for no known reason he had an attack of palpitation, and the evening pulse became very rapid from that time. Taken, however, during the night 53–54 while he was asleep the pulse-rate was only 76, though it had been 116 in the evening.

many relapses, or the temperature did not settle down after the relapses ceased, or there was a prolonged initial fever. But in some there was no evidence of any special severity.

It is evident that the heart is so far affected with the virus of trench fever that it sometimes accelerates even though the patient remains in bed, and still more often if any slight strain such as that of getting up is put upon it. It is well known that this tachycardia may be of very long duration.

2. Dilatation of the Heart. Tachycardia is sometimes followed by dilatation of the heart, shown by a change in position of the apex beat. In several cases we have watched the apex pass from the normal position until it was palpable from $\frac{1}{4}$ inch even up to 1 inch outside the nipple line. In some of these we have seen it return to its normal place.

A *mitral systolic bruit*, usually faint but once at least of a musical character, has developed under observation in fourteen cases. It has always disappeared within a few days. We have never seen any evidence of endocarditis.

In nine cases *praecordial pain* has appeared. In one or two it has extended to the neck and left arm. It disappeared in about twenty-four hours, and was seldom felt more than once.

3. Tremor. *Fine tremor of the hands* with sweating of the palms has been noticed in eight cases. It resembles that seen in exophthalmic goitre and is seen in cases which have tachycardia. There is, however, no goitre or exophthalmos, and the symptom is of short duration though it may be seen on more than one occasion.

4. Systolic Blood Pressure. Although the conditions of our work have prevented any large series of continuous observations, we have been able to make 520 estimations of the systolic pressure on 191 patients. We used a wide R.R. arm-piece and estimated by the auscultatory method.

Observations taken in successive weeks of the disease produce the following results:

1st week.	74 observations	. . . . .	Av. S. P. 119
2nd „	115 „	. . . . .	„ „ 119·5
3rd „	94 „	. . . . .	„ „ 121·6
4th „	61 „	. . . . .	„ „ 127·5
5th „	44 „	. . . . .	„ „ 130·7
6th „	26 „	. . . . .	„ „ 121
7th „	24 „	. . . . .	„ „ 129
8th „	7 „	. . . . .	„ „ 134
9th „	4 „	. . . . .	„ „ 139

In some patients we were able to make several observations.

TABLE.

Case	Ref.	1st week.	2nd week.	3rd week.	4th week.	5th week.	6th week.	7th week.	8th week.	Over 8th week.
A. 1.	36		115	108	105	125 120 145				
	112	120	110	110 112	115	125				
	115	135	125	110		125				
	116	120	120 110	123 120				135		
	118		110 120	120		127				
	121		110	105		110				
	123	115		115	130					
	124	95	100			95	95		115	
	128				120	115			120	
	129			105	110			115		
	130	118	100	105	125					
	131	100	115	120		130				
	133		130	128	122	142				
	140		100		110	128				
	144		100		110	128	115	127	122	
	145	95	105	112 125	118	117		105		
	146			130	115	127				
	147	110	105		110					
A. 2.	57	127	117				130 130	125		
	58				125	120		115		
	59		110			115		110	120	
	60	105	110	107			115			
	61	130 115				105	105		118	118
	62				105	125	128			
	63	120		127			127		120	
	64	133	125	135			130		120	
B.	18				115	130		120		
	25	115		120	125					
	28[1]					135			180	170
	32	100	120 120	112			128			
	33[2]		145 145	130			150			
	34		130 145	140			125			
	35	125 122	130 122			135				
	36[3]	140	140	140		145	145			
	40		115		125	145				
	43			120	120	128				
	53	132		130	130					
	61	120 110	117				130	125		
	62	125	127	130				125	125	
	65	120		110		132				
	66	100	112		122					
C.	32[4]					130		110	170	
	41	122		95	112					

[1] B. 28 was 19 years of age, otherwise healthy. He had no fever after his admission (2nd day), but prolonged pain and a certain amount of tachycardia after getting up.

[2] B. 33 was 24 years of age, otherwise healthy. He had a considerable amount of fever and prolonged pain, but very slight tachycardia.

[3] B. 36 was 39 years of age.

[4] C. 32 was 33 years of age, otherwise healthy. His temperature was never above 99° after the 10th day. He had prolonged pain, and tachycardia along with sweating and tremulous hands.

TABLE (*continued*)

Case Ref.	1st week.	2nd week.	3rd week.	4th week.	5th week.	6th week.	7th week.	8th week.	Over 8th week.
C. 47[5]		115	134				160		
54	108	125	120			125			
59[6]		145		150	170				
61	118, 122			125	120				
63[7]	135		135	175					
77	140	120	125, 125						
78		110	100	100, 125					
82	130	110, 125	120						
85	110	105, 105	100, 130						
86		120	125	130					
87	107	105, 115	115	120		135			
88[8]		127				130	148		140
89	112	122	120			110			
90		115					135		130
91		128	125			135			
92		128	128	115		128	128		

[5] C. 47 was 24 years of age, otherwise healthy. He had fever for 23 days and prolonged pain. The heart was dilated, but there was no tachycardia.

[6] C. 59 was 25 years of age. His fever lasted only 8 days and he had practically no pain after the 5th day. He had tachycardia, and the heart was dilated. The radial artery was thickened. There was no albuminuria.

[7] C. 63 was 21 years of age, otherwise healthy. He had a very slight illness with fever for 6 days only.

[8] C. 88 was 32 years of age, otherwise healthy. He had fever with pains up to the 39th day. After this he had considerable tachycardia, slight dilatation of the heart, praecordial pain, and tremor of the hands.

There are few cases in this table which show much increase in the blood pressure, but on the whole the tendency is to a slight rise, and in some, which are noted above, to a remarkable increase.

5. CARDIAC REACTION TO ATROPIN. The atropin reaction on which Marris has written was tested seventy times on forty-four patients, four of whom were examined three times. The test proved positive in ten patients, of whom six gave the positive reaction once out of two tests, and four twice out of three tests each. The remainder of the tests proved negative. These cases were all carefully tested both bacteriologically and serologically by Perkins. Two of them were used in order to produce trench fever in volunteers by inoculation of blood. Apparently, therefore, the atropin test is positive, that is the 'escape' of the heart is prevented, in about a quarter of those patients who have trench fever.

NOTE.—Since writing these notes we have had the opportunity of seeing a large number of cases of influenza during the epidemic. We have noted nystagmus to be frequent at onset, and during the febrile period. But it has not persisted, or reappeared in a febrile period, as was the case in trench fever. We have also noticed enlargement of the spleen in about 10 per cent. of influenzal cases. It was much more frequent and lasted much longer in trench fever.

A STUDY OF THE HAEMATOLOGY OF TRENCH FEVER

By HERBERT W. PERKINS and R. H. URWICK

When the disease now commonly known as trench fever was first recognized in the British Expeditionary Force the regularly relapsing character of the temperature charts suggested that the cause of the condition might be found in an examination of the blood.

McNee and Renshaw (1) in an experimental study of the disease were the first to prove that the infecting agent, whatever its nature, was present in the circulating blood. Their observations, confirmed in all essential particulars by other investigators, stimulated research wherever the disease was met with, and during the past two years the causative organism has been sought in blood films by very many observers.

Opportunities have arisen during the investigation of trench fever carried on during the past few months under the auspices of the Trench Fever Committee in France for a careful examination of the blood at all stages of the disease.

It has been possible to retain cases under observation for a period of several weeks, a condition favouring research, which, for many reasons, has been impossible for other workers.

In this investigation endeavours have been made (1) to identify the causative organism in films; (2) to study the morphology of the blood elements during the disease; (3) to determine by repeated enumeration and differentiation of the cells present in the blood during the various phases of the disease whether or no there exists a blood picture characteristic of the disease or of diagnostic significance.

In the examination of blood films several methods of staining have been employed, but as a routine measure Leishman's stain has been adopted.

Cells have been counted on a Thoma Zeiss stage and haemoglobin estimations made with a Gower's apparatus. The latter, as an instrument of precision, leaves much to be desired, but in the absence of facilities for procuring coal gas, was the most accurate obtainable.

Blood films from several hundred cases have been examined and the blood count has been carefully followed through in over fifty. The counts in the latter cases have always been made at the same hour of the day (11 a.m.–12.30 p.m.), and have been repeated as often as possible—daily in many cases.

The examination of blood films has so far thrown no light on the aetiology of the disease.

From time to time several observers have claimed to have found in them

[Q. J. M., July, 1918.]

organisms to which they have attributed an aetiological significance. Reimer (2) is credited with having described a spirochaete in the blood; Jungmann and Kuczynski (3), using Giemsa's stain, have observed dumb-bell shaped organisms; Dimond (4), the flagellates he described as haemogregarines, and Pappenheimer small discoid bodies.

Of the organisms mentioned above, Dimond's flagellates are the only ones that have been recognized during this investigation. In Ross films laked with distilled water they have frequently been met with, but they also are found in similar films of normal blood. They play no part in the causation of the disease and, as was shown by Henry, their occurrence in films can be explained by their presence in the distilled water employed in their preparation.

A study of the morphological changes observed in films has contributed nothing which can be considered of diagnostic importance.

One of the most striking characteristics of the blood in trench fever, especially of films taken during a relapse, is the presence, often in great numbers, of the *corps en demi-lune* described in association with this disease by Renaux (5). They are not peculiar to trench fever but occur in other conditions associated with high fever. They have been found during this investigation in blood taken for control purposes from patients suffering with pneumonia and have also been described in association with malaria.

Punctate basophilia of the red corpuscles has been described by McNee and Renshaw as a constant feature of the blood in this disease. They associate its incidence with the anaemia which accompanies the condition. It has been noted in only a few cases of those dealt with in this communication, and therefore as a diagnostic feature must be considered to be of but little value. In a much larger proportion of cases very large pale red corpuscles are found. In films stained with Leishman's stain these have a yellowish colour.

No attempt has been made to enumerate the blood platelets, but a very definite impression remains that they are increased both in number and size. This increase appears to be most pronounced during the febrile periods. There is nothing which peculiarly characterizes the leucocytes in this disease, but in many cases associated with high fever the nucleus of the polymorphonuclear cell has appeared to be unusually lobose. Attention has been called by others to the anaemia which accompanies trench fever.

In the present investigation, cases in the early weeks of the disease are alone included. At this period anaemia is not clinically a recognizable symptom, but an enumeration of the red cells and an estimation of the haemoglobin confirm the observations of McNee and Renshaw, who found a definite defect in the percentage of haemoglobin, but no loss in the number of red corpuscles. In this series the red count has averaged five and a half million corpuscles; a percentage of haemoglobin below eighty has never been recorded—a common average is ninety.

It is difficult without burdening this communication with much detail to place on record all the results of the blood counts made during this investigation.

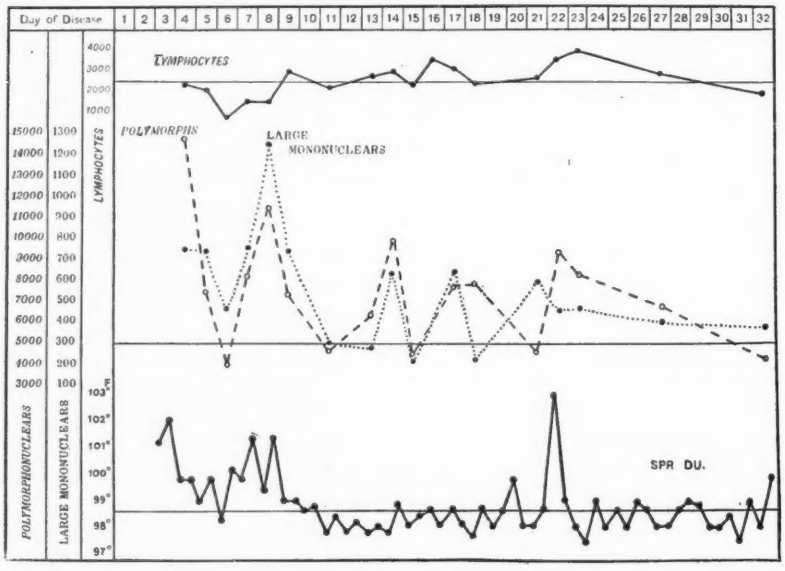


CHART 1. Spr. Du. Age 29. 2–8. Severe pains, with pink eyes. 9–11. Felt better. 12–20. Considerable pain. Bad in shins on 14th day. 21–26. Pains occasional. 27–29. Headache. Nystagmus and pink eyes. 30–32. Rather better. Pulse followed temperature and kept low. Spleen felt from admission to evacuation 48th day.

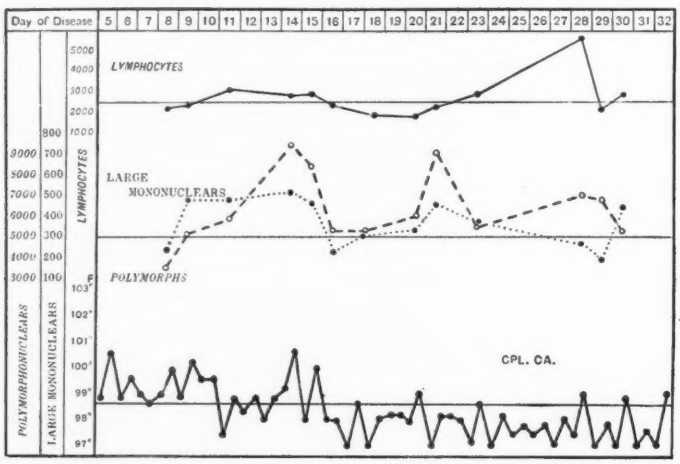


CHART 2. Cpl. Ca. Age 25. 5–8. Pains in shins. 9–10. Felt well. A few spots each day. 11–13. Felt well. 14–15. Return of headache and pain in shins. 19–27. Feeling very well. 28. No pains.

The pulse was irregular. It varied closely with the temperature till 16th day, when it rose to 90 in the evening. Thence onward it varied from 72 to 100.

He got up for a few hours first on 24th day. The spleen was palpable from admission to 33rd day. Discharged 42nd day.

Twelve illustrative cases have therefore been selected and the results have been presented in chart form.

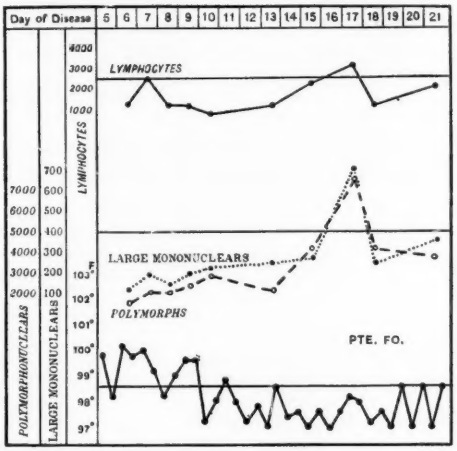


CHART 3. Pte. Fo. Age 25. 5–6. Shin pains and backache. 7–8. Felt better. 9. Headache, pain in back and legs. 13. Pain in back and thighs. 17. Pain in back and hips. 18–21. Pains better. Feels and looks better. The pulse followed the temperature until 16th day, when it rose over 80 and lay between 80 and 90 until 22nd day. Spleen palpable from admission to 27th day. Discharged 50th day.

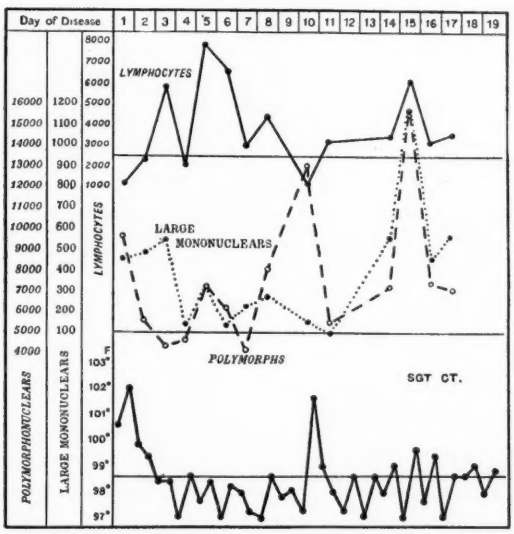


CHART 4. Sgt. Ct. Age 28. Spots seen on admission 7 hours after onset. 4–9. Felt perfectly well.

These charts depict fluctuations as they occur in three types of leucocytes only, viz. in the polymorphonuclears, the lymphocytes (including both large and small varieties), and in the large mononuclear cells.

Except in a few cases, to which reference will be made later, the other cells of the blood—the transitionals, the eosinophils, and the basophils—showed but such slight variations that all record of these has been omitted.

The numbers of cells of two out of the three types represented are charted, about a separate normal line for each kind of cell.

This line for the polymorphonuclear cells represents a count of 5,000 cells per cmm.; for the lymphocytes 2,500 per cmm.

At the foot of each chart is a record of the temperature during the disease.

In the note the date-numbers refer to the day of the disease.

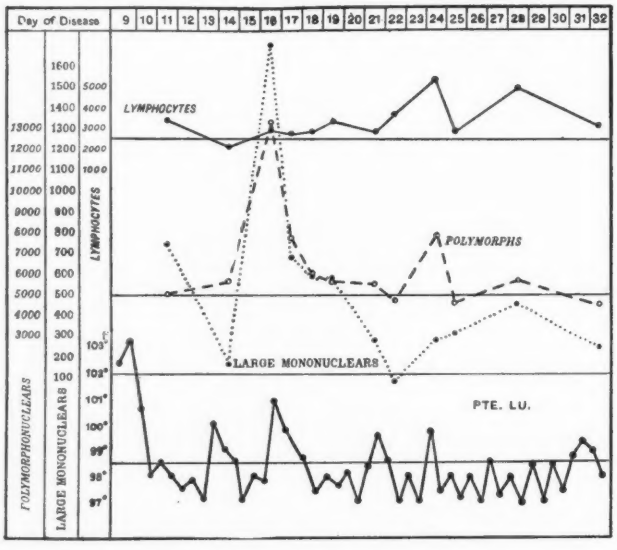


CHART 5. Pte. Lu. Age 28. Admission 9th day, probably in relapse. Pains till 13th. 15. Feeling well. 16–18. Bad pains. 22. Head pains. Vomited. 23. No pain. 24–26. Slight pain. 29. Pains. Spots, which returned afresh 30th, 32nd, and 33rd days. 30–32. Headache but no other pain. Headache and pains finally ceased on 43rd day. There was some tachycardia from 23rd day (while still in bed) till 47th day. The spleen was felt from admission to 13th, and from 17th to 20th days. Discharged 52nd day.

A study of the blood counts recorded during this investigation apparently justifies the following conclusions:

1. Generally speaking the disease is associated with a leucocytosis.

The polymorphonuclear cells and the lymphocytes are nearly always present in more than normal numbers; very occasionally, during an afebrile period, their number may be diminished.

2. There is, as a rule, a marked rise in the number of leucocytes present in the blood at the time of a febrile relapse. This rise sometimes precedes the fever, sometimes accompanies it, sometimes follows it.

3. Occasionally there is a similar rise in the number of leucocytes without

any corresponding rise in temperature. This rise suggests a relapse and is frequently associated with an exacerbation of the patient's symptoms.

4. Subject to exceptions which occur in but very few instances, there is during a febrile period a simultaneous increase in number of both the polymorphonuclear and lymphocyte cells. Relatively this increase is greater in the case of the polymorphonuclear cells than in that of the lymphocytes.

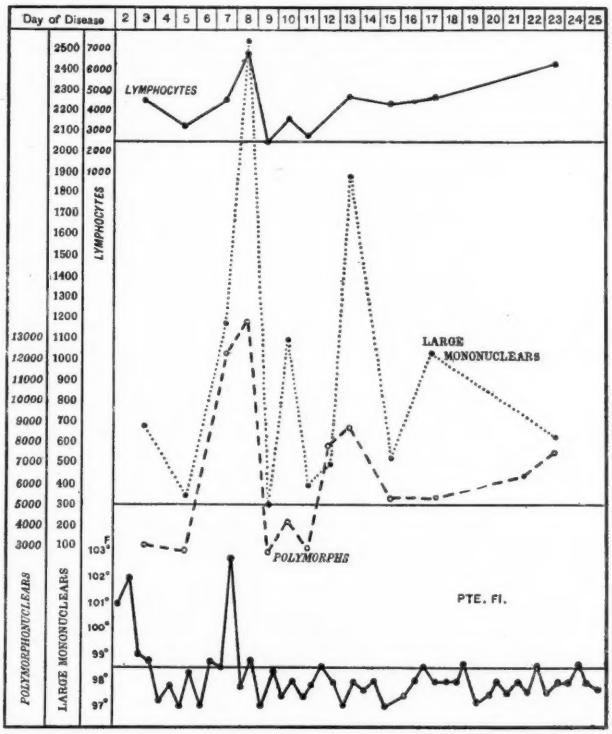


CHART 6. Pte. Fi. Age 19. 4–6. No pain. Felt well. 7. Chills. Headache. After this he felt quite well. Spots seen on 14th day (leucocytosis). Pulse-rate below 80 9th–13th days, rose to 80 14th–16th, over 80 19th–21st days. Spleen felt from admission to 19th day. Discharged 31st day. A slight case.

5. During convalescence the number of lymphocytes present in the blood relatively increases.

6. Variations occurring in the number of the large mononuclear cells closely correspond with those affecting the polymorphonuclear and lymphocyte counts.

With reference to the cells of the blood not included in the charts, the transitionals and the basophils present no marked variation from a normal standard.

In a few cases a pronounced eosinophilia has been met with, the number of eosinophils present varying greatly from day to day. No cause could be assigned for this condition nor for the marked fluctuation in numbers which accompanied it.

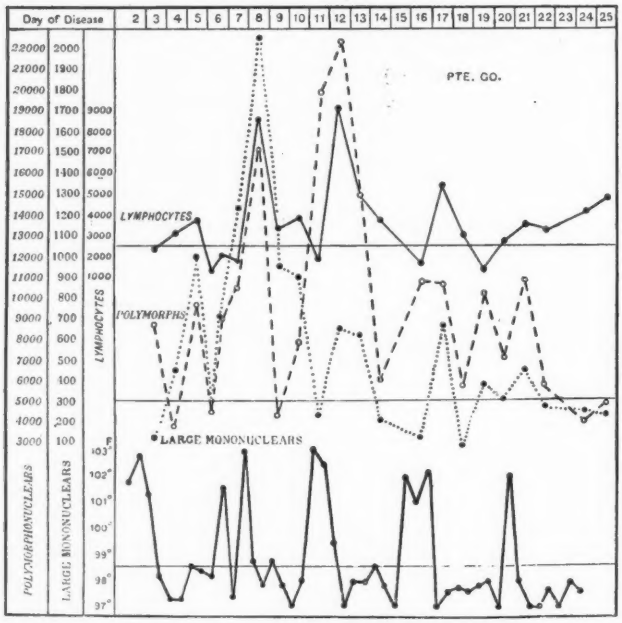


CHART 7. Pte. Go. Age 19. 2–6. Pains. 7. Felt well. 8–9. Headache. 10. Felt well. 11. Headache. Spots. 12–14. No symptoms. 15–16. Headache. Spots on 15th day. 17–18. Felt well. 19–20. Headache. Spots on 19th day. Hyperalgesia 10th D. root-zones on 20th day. 21–23. Felt well. 24. Headache. 26. Felt well. 29. Discharged.

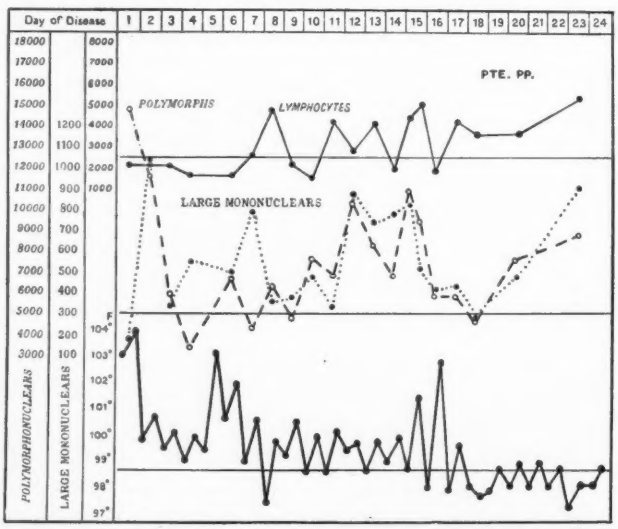


CHART 8. Pte. Pp. Age 23. Fever with irregular relapses lasted 17 days. Spots were seen on the 2nd and 14th days. Nystagmus on the 11th and 15th–18th days. After this, though there was no fever, he complained repeatedly of pain, and nystagmus lasted with occasional intermissions to the 29th day. The pulse followed the temperature. The spleen was felt on 3rd–7th days. Discharged 39th day. A severe case.

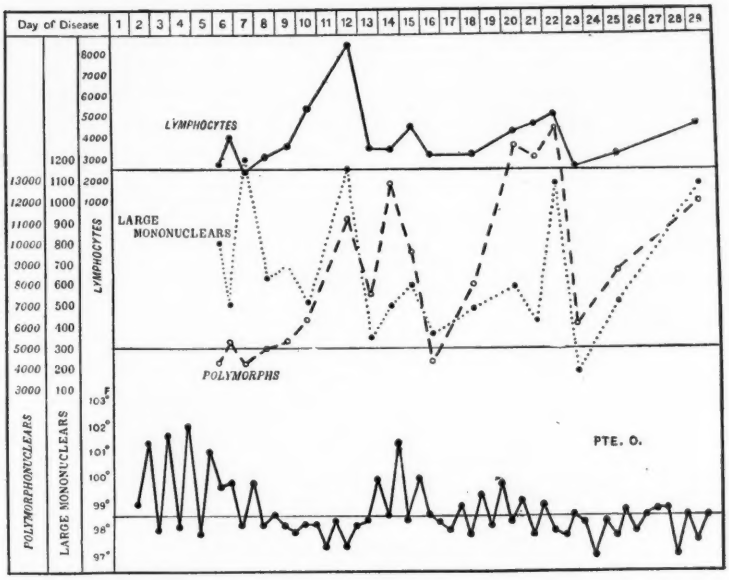


CHART 9. Pte. O. Age 30. 1–6. Nystagmus and shin pains 7–13. Felt well with occasional slight pains, until afternoon of 13th day, when symptoms occurred. 13–21. Pains almost every day. 22. No pains. The pulse followed the temperature. Spleen felt from admission to discharge 51st day.

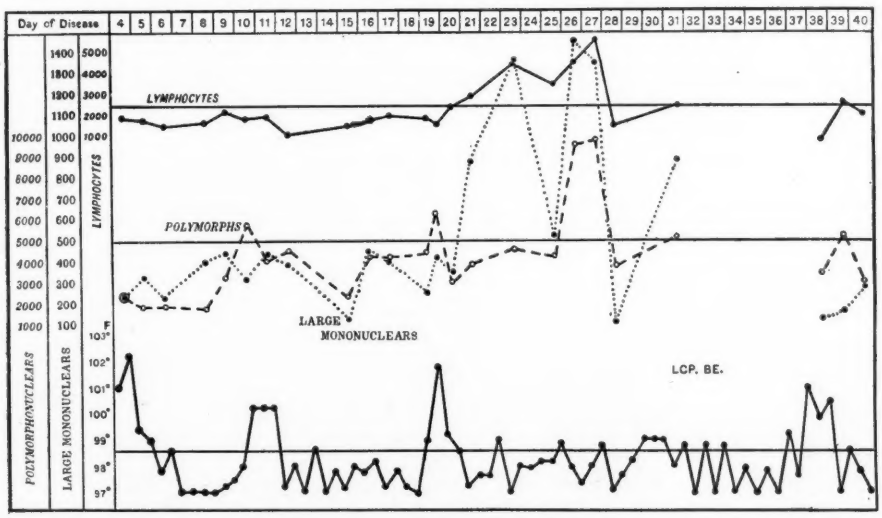


CHART 10. Lcp. Be. Age 22. 4. Pains. 5–9. No symptoms. 10–12. Headache. Nystagmus on 10th, spots on 11th day. 13–15. No symptoms. 16. Hyperalgesia 10th D. root-zones. 19. Headache and pains. Spots. Nystagmus, which lasted till 23rd day and returned on 25th and 28th days. 20–27. No symptoms, but nystagmus. 28–31. Pains. 36–38. Headache and pains. The pulse followed the temperature. The spleen was felt from admission to 33rd day, and again 38th–44th days. Discharged 68th day. A severe case.

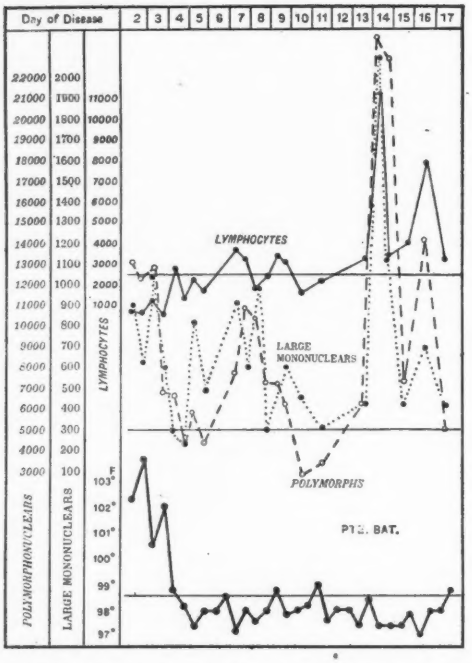


CHART 11. Pte. Bat. Age 23. 2–3. Pains. 4–5. Better. 6–9. Slight pains and headache. 10. No pain. 11–13. Headache and pains. 14–20. Still slight pains. No cause obvious for great leucocytosis. 21. Felt well. The pulse was low throughout. The spleen was felt from admission to 15th day. Discharged 39th day.

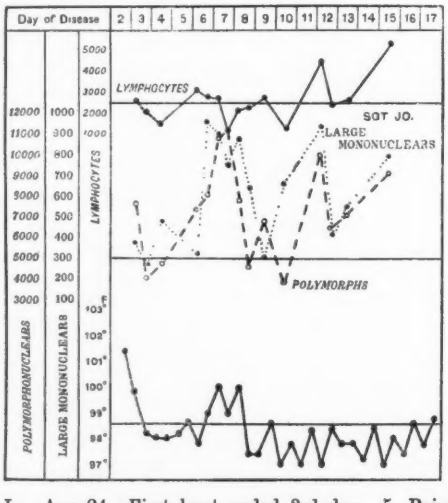


CHART 12. Sgt. Jo. Age 24. First bout ended 3rd day. 5. Pains returned and lasted till 10th day. Nystagmus on 7th and 8th days. 12. Feeling well. 14. Headache and slight nystagmus, which lasted over 15th day. The pulse-rate was low, 70–80 after the 5th day. The spleen was felt from admission to 20th day. Discharged 41st day.

Conclusions.

1. There is no appearance in blood-films which is characteristic of the disease.

2. A single enumeration and differentiation of the leucocytes is often of value as a means of diagnosis from enteric, but cannot afford any reliable evidence that the disease present is trench fever.

3. Repeated counts carried on through the various phases of the disease produce a composite picture which, though not without exceptions, is so constant that it may be considered characteristic. It consists in the combination of the following features:

(*a* A marked rise of leucocytes of all three kinds (polymorphs, lymphocytes, and large mononuclears) at the time of a febrile relapse.

(*b*) A gradual relative rise in the lymphocytes during the period of convalescence.

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